(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 March 2016 (24.03.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/041470 A1

(51) **International Patent Classification**:
C07D 307/10 (2006.01) ***A61K 31/351*** (2006.01)
C07D 307/30 (2006.01) ***A61P 3/10*** (2006.01)
C07H 7/04 (2006.01)

(21) **International Application Number**:
PCT/CN2015/089492

(22) **International Filing Date**:
14 September 2015 (14.09.2015)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
PCT/CN2014/086527
15 September 2014 (15.09.2014) CN

(71) **Applicant**: **NATIONAL INSTITUTE OF BIOLOGICAL SCIENCES, BEIJING** [CN/CN]; 7 Science Park Rd., ZGC life science park Changping District, Beijing 102206 (CN).

(72) **Inventors**: **ZHANG, Zhiyuan**; 7 Science Park Rd., ZGC life science park Changping District, Beijing 102206 (CN). **HUANG, Shaoqiang**; 7 Science Park Rd., ZGC life science park Changping District, Beijing 102206 (CN). **ZHANG, Zhaolan**; 7 Science Park Rd., ZGC life science park Changping District, Beijing 102206 (CN). **SU, Yaning**; 7 Science Park Rd., ZGC life science park Changping District, Beijing 102206 (CN). **REN, Yan**; No. 7 Science Park Rd., ZGC life science park Changping District, Beijing 102206 (CN).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2016/041470 A1

(54) **Title**: SGLT-2 INHIBITORS

(57) **Abstract**: Provided are compounds of SGLT-2 inhibitors, pharmaceutically acceptable salts, hydrides and stereoisomers thereof. The compounds are employed in pharmaceutical compositions, and methods of making and use, including treating a person in need thereof with an effective amount of the compound or composition, and detecting a resultant improvement in the person's health or condition.

SGLT-2 Inhibitors

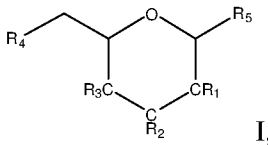
Inventors: Zhiyuan Zhang, Shaoqiang Huang, Zhaolan Zhang, Yaning Su, Yan Ren, all of Beijing, CN
Assignee: National Institute of Biological Sciences, Beijing
Priority Claim: PCT/CN2014/086527; Filed: Sep 15, 2014; Sub No. 010637

[001] Introduction

[002] Sodium-D-glucose co-transporter 2 (SGLT-2) inhibitors provide drugs for treating diabetes and obesity, inter alia, e.g. Diabetes, 1999, 48, 1794-1800, Dapagliflozin (Diabetes, 2008, 57, 1723-1729). Various O-aryl and O-heteroaryl glycosides have been reported as SGLT-2 inhibitors, e.g. WO 01/74834, WO 03/020737, US04/0018998, WO 01/68660, WO 01/16147, WO 04/099230, WO 05/011592, US 06/0293252 and WO 05/021566. Various glucopyranosyl-substituted aromatic and heteroaromatic compounds have also been reported as SGLT-2 iinhibitors, e.g. WO 01/27128, WO 04/080990, US 06/0025349, WO 05/085265, WO 05/085237, WO 06/054629 and WO 06/011502. Other publications include: US 7838498; US 8586550; WO 2012172566; WO2013191549; US2006074031; US8,614,195; US20060074031; US20080004336; WO2005012326.

[003] Summary of the Invention

[004] In an aspect the invention provides glucopyranoside compounds of formula I:



[005] I,

[006] wherein:

[007] one of R1-R3 is oxo and two of R1-R3 are independently H, F, –OR6, wherein each R6 is independently H, methyl or acetyl (CH_3CO-);

[008] R4 is H, F or OR7, where R7 is H, methyl or acetyl (CH_3CO-);

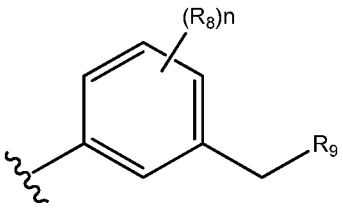
[009] R5 is aryl or heteroaryl, or a salt or acetate thereof.

[010] Encompassed are all combinations of particular embodiments:
wherein R2 or R3 is oxo; R2 is oxo; two of R1-R3 are independently F or –OR6, wherein each R6 is independently H, methyl or acetyl (CH_3CO-), and R4 is F or OR7, wherein R7 is H, methyl or acetyl (CH_3CO-); two of R1-R3 are independently –OR6, wherein each R6 is independently H, methyl or acetyl (CH_3CO-), and R4 is OR7, wherein R7 is H, methyl or acetyl (CH_3CO-); two of R1-R3 are independently –OR6, wherein each R6 is H or acetyl (CH_3CO-),

and R4 is OR7, wherein R7 is H or acetyl (CH_3CO-); and/or two of R1-R3 are independently –OR6, wherein each R6 is H, and R4 is OR7, wherein R7 is H;

[011] wherein R5 is substituted phenyl;

[012] wherein R5 is substituted phenyl of formula:

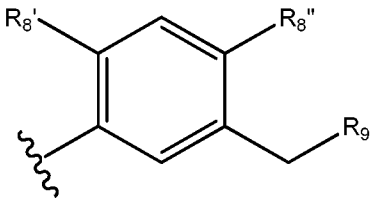


[013]

[014] wherein each R8 is a hydrocarbon or heteroatom-containing functional group (non-hydrogen substituent), R9 is aryl and n is 0, 1, 2, 3 or 4, wherein R8 can also bind C1 of the glucopyranoside ring (e.g. MeO forming an ether);

[015] wherein each R8 is independently substituted or unsubstituted lower alkyl (e.g. Me), lower alkenyl, lower alkynyl (e.g. ethynyl), alkyloxy (e.g. OMe, OEt), halide, hydroxyl, carbonyl, aldehyde, carboxyl, ester, acetal, carboxamide, amine, imine, azide, azo, cyanate, nitrate, nitrile, nitro, nitroso, sulfydryl, sulfide, sufone, thocyanate, phosphine, phosphate, etc.;

[016] wherein R5 is substituted phenyl of formula:



[017]

[018] wherein $(R8)_n$ is R8' and R8" and

[019] R8" is H, halide, lower alkyl (e.g. Me or Et), lower alkenyl, lower alkynyl (e.g. ethynyl), alkyloxy (e.g. OMe or OEt), and

[020] R8' is H, halide, lower alkyl (e.g. Me or Et), lower alkenyl, lower alkynyl (e.g. ethynyl), alkyloxy (e.g. OMe or OEt), wherein the alkyloxy (e.g. OMe or OEt) also binds C1 of the glucopyranoside ring;

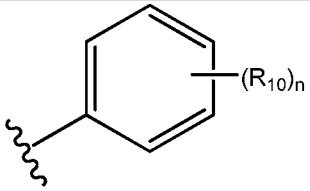
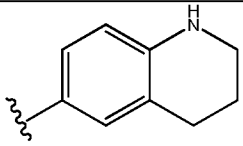
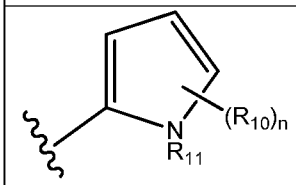
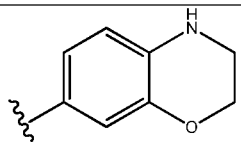
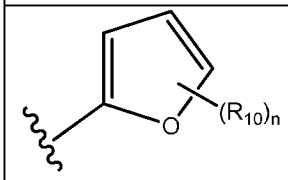
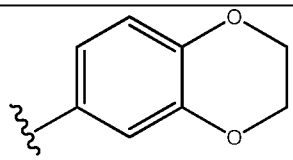
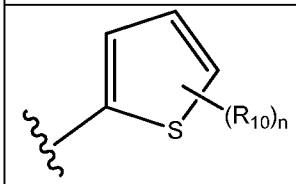
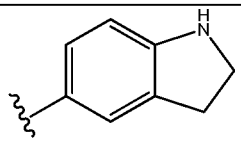
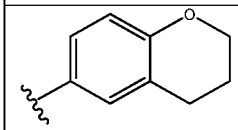
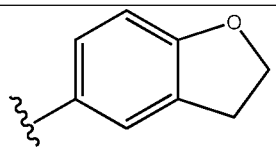
[021] wherein R9 is substituted or unsubstituted, homo- or hetero, 5- or 6-membered cyclic or 9 or 10 membered bi-cyclic aryl;

[022] wherein R9 is substituted or unsubstituted:

phenyl,	benzopiperidin-6-yl,
pyrrol-2-yl,	3,4-dihydro-2H-benzo[b][1,4]oxazine-7-yl
furan-2-yl,	2,3-dihydrobenzo[b][1,4]dioxin-6-yl,
thiophen-2-yl,	Indolin-5-yl, or 5-indolinyl

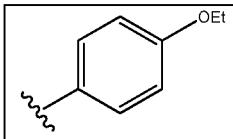
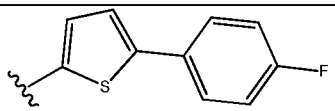
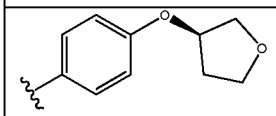
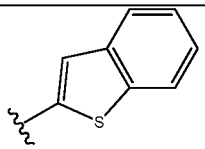
chroman-6-yl,	2,3-dihydrobenzofuran-5-yl;

[023] and/or as depicted:

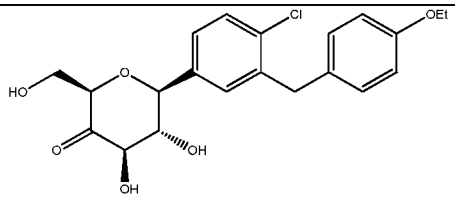
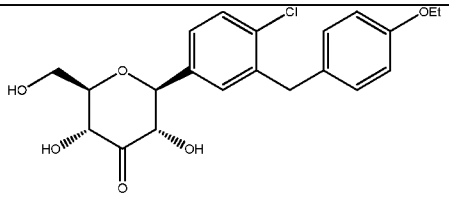
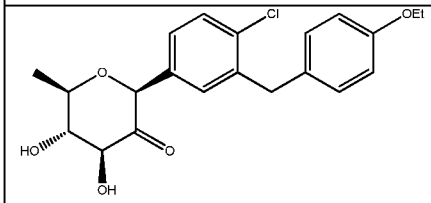
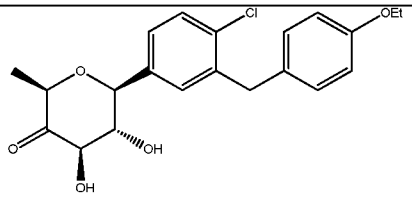
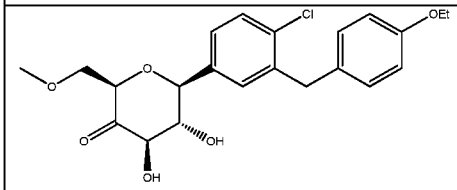
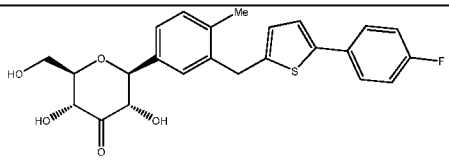
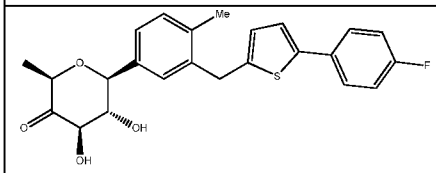
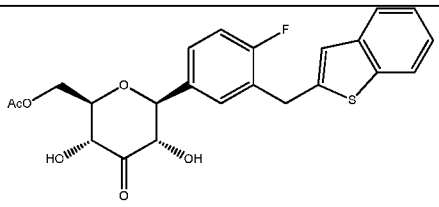
 phenyl	 benzopiperidin-6-yl
 Pyrrol-2-yl	 3,4-dihydro-2H-benzo[b][1,4]oxazine-7-yl
 Furan-2-yl	 2,3-dihydrobenzo[b][1,4]dioxin-6-yl
 Thiophen-2-yl	 Indolin-5-yl, or 5-indolinyl
 chroman-6-yl	 2,3-dihydrobenzofuran-5-yl;

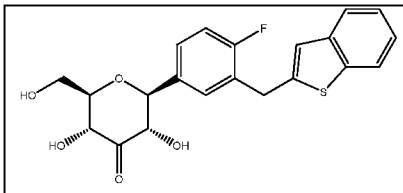
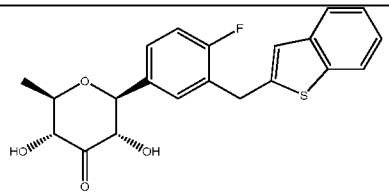
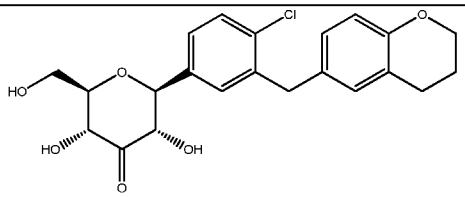
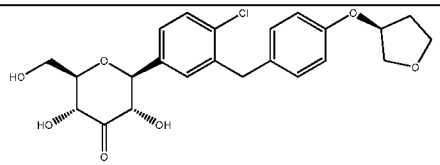
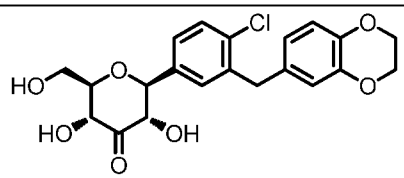
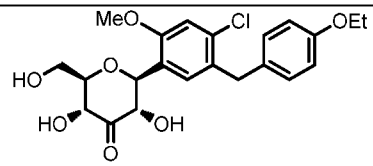
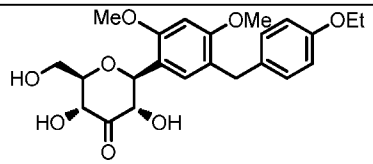
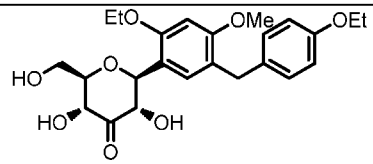
[024] wherein each R10 is a hydrocarbon or heteroatom-containing functional group (non-hydrogen substituent), including alkyl or heterolkyl, alkyloxy or heteroalkyloxy, including cyclic forms of each, and such as independently substituted or unsubstituted (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_1-C_4)alkyloxy, 3-oxetanyloxy, 3-tetrahydrofuranyloxy, halide, fluoro-substituted (C_1-C_2)alkyl, (C_1-C_4)alkyl-SO_2-, (C_3-C_6)cycloalkyl, or a (C_5-C_6)heterocycle having 1 or 2 heteroatoms each independently selected from N,O, or S, such as Cl, F, hydroxyl, carbonyl, aldehyde, carboxyl, ester, acetal, carboxamide, amine, imine, azide, azo, cyanate, nitrate, nitrile, nitro, nitroso, sulfydryl, sulfide, sufone, thocyanate, phosphine, phosphate, etc.;

[025] wherein R9 is:

 4-ethoxyphenyl;	 4-fluorophenyl thiophen-2-yl;
 tetrahydrofuran-3-yloxy-phenyl; or	 benzo[b]thiophen-2-yl;

[026] wherein the compound of claim 1 of formula:

 4;	 5;
 6;	 7;
 8;	 10;
 11;	 12;

 13;	 14;
 16;	 18;
 20;	 21;
 22;	 23.

[027] In another aspect the invention provides 2-aryl, 6-methyl-B-dihydro-pyran-one compounds, wherein the methyl may be substituted.

[028] Encompassed are all combinations of particular embodiments supra and here:

[029] wherein the compound is a 3-oxo-glucopyranoside or 4-oxo-glucopyranoside.

[030] wherein the aryl is substituted phenyl;

[031] wherein the aryl is 3-(methyl-aryl)5-(lower alkyl) phenyl, wherein the methyl-aryl is methyl-(substituted or unsubstituted, homo- or hetero, 5- or 6-membered cyclic or 9 or 10 membered bi-cyclic aryl);

[032] wherein the aryl is 3-(methyl-aryl)5-(lower alkyl) phenyl, wherein the methyl-aryl is methyl-(

phenyl,	1,2,3,4-tetrahydroquinolin-6-yl,
pyrrol-2-yl,	3,4-dihydro-2H-benzo[b][1,4]oxazine-6-yl
furan-2-yl,	2,3-dihydrobenzo[b][1,4]dioxide-6-yl,
thiophen-2-yl,	Indolin-5-yl, or

chroman-6-yl,	2,3-dihydrobenzofuran-5-yl);

[033] wherein the aryl is: 4-ethoxyphenyl; 4-fluorophenyl thiophen-2-yl; benzo[b]thiophen-2-yl; tetrahydrofuran-3-yloxy-phenyl; or chroman-6-yl-phenyl.

[034]

[035] In another aspect the invention provides an acetate of a disclosed compound, or salt thereof.

[036] In another aspect the invention provides a compound of any of the Tables herein, or an acetate thereof, or a salt thereof, particularly a pharmaceutically acceptable salt, or a hydride or stereoisomer thereof.

[037] In embodiments the invention provides a disclosed compound that is a sodium-glucose linked transporter-1 (SGLT2) inhibitor.

[038] In embodiments the invention provides a pharmaceutical composition comprising a disclosed compound in unit dosage form, and/or coformulated or copackaged or coadministered with a different anti-diabetes drug

[039] The invention also provides methods of using a disclosed compound or composition comprising administering it to a person determined to be in need thereof, and optionally, detecting a resultant therapeutic effect.

[040] The invention provides pharmaceutical compositions comprising the subject compounds, and methods of making and using the subject compounds, including methods of inhibiting SGLT-2. The compositions may comprise a pharmaceutically-acceptable excipient, be in effective, unit dosage form, and/or comprise another, different therapeutic agents for the targeted disease or condition. In embodiments, the invention provides methods of treating a person in need thereof with an effective amount of the subject compound or pharmaceutical composition, and optionally, detecting a resultant improvement in the person's health or condition. The methods may also optionally include the antecedent step of determining that the person, particularly diagnosing and applicable disease or condition (herein).

[041] The invention encompasses all combination of the particular embodiments recited herein.

[042] **Brief Description of the Drawings**

[043] Fig. 1 Single oral doses of Example 5 reduce blood glucose in ZDF rats over 24-h.

[044] Fig. 2 Single oral doses of Example 5 increase urine volume and urinary glucose excretion in ZDF rats over 24-h.

[045] Description of Particular Embodiments of the Invention

[046] The following descriptions of particular embodiments and examples are provided by way of illustration and not by way of limitation. Those skilled in the art will readily recognize a variety of noncritical parameters that could be changed or modified to yield essentially similar results.

[047] The invention provides 2-aryl, 6-methyl-B-dihydro-pyran-one compounds and related articles, compositions, formulations, methods of making and methods of using. The invention provides myriad embodiments, as detailed herein.

[048] Applicable diseases or conditions are mediated at least in part through SGLT-2 activity and ameliorated or treatable at least in part by inhibiting SGLT-2, and include diabetes and obesity.

[049] Unless contraindicated or noted otherwise, in these descriptions and throughout this specification, the terms “a” and “an” mean one or more, the term “or” means and/or and polynucleotide sequences are understood to encompass opposite strands as well as alternative backbones described herein. Furthermore, genuses are recited as shorthand for a recitation of all members of the genus; for example, the recitation of (C1-C3) alkyl is shorthand for a recitation of all C1-C3 alkyls: methyl, ethyl and propyl, including isomers thereof.

[050] The term "heteroatom" as used herein generally means any atom other than carbon or hydrogen. Preferred heteroatoms include oxygen (O), phosphorus (P), sulfur (S), nitrogen (N), and halogens, and preferred heteroatom functional groups are haloformyl, hydroxyl, aldehyde, amine, azo, carboxyl, cyanyl, thocyanyl, carbonyl, halo, hydroperoxyl, imine, aldimine, isocyanide, iscyante, nitrate, nitrile, nitrite, nitro, nitroso, phosphate, phosphono, sulfide, sulfonyl, sulfo, and sulfhydryl.

[051] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which is fully saturated, having the number of carbon atoms designated (i.e. C1-C8 means one to eight carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl and the like.

[052] The term "alkenyl", by itself or as part of another substituent, means a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (i.e. C2-C8 means two to eight carbons) and one or more double bonds. Examples of alkenyl groups include vinyl, 2-propenyl,

crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl) and higher homologs and isomers thereof.

[053] The term "alkynyl", by itself or as part of another substituent, means a straight or branched chain hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (i.e. C2-C8 means two to eight carbons) and one or more triple bonds. Examples of alkynyl groups include ethynyl, 1- and 3-propynyl, 3-butynyl and higher homologs and isomers thereof.

[054] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from alkyl, as exemplified by $-CH_2-CH_2-CH_2-CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[055] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

[056] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, P, Si and S, wherein the nitrogen, sulfur, and phosphorous atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2,-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH3)-CH_3$. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

[057] Similarly, the term "heteroalkylene," by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

[058] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Accordingly, a cycloalkyl group has the number of carbon atoms designated (i.e., C3-C8 means three to eight carbons) and may also have one or two double bonds. A heterocycloalkyl group consists of the number of carbon atoms designated and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyrid- yl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[059] The terms "halo" and "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include alkyl substituted with halogen atoms, which can be the same or different, in a number ranging from one to (2m'+1), where m' is the total number of carbon atoms in the alkyl group. For example, the term "halo(C1-C4)alkyl" is mean to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. Thus, the term "haloalkyl" includes monohaloalkyl (alkyl substituted with one halogen atom) and polyhaloalkyl (alkyl substituted with halogen atoms in a number ranging from two to (2m'+1) halogen atoms, where m' is the total number of carbon atoms in the alkyl group). The term "perhaloalkyl" means, unless otherwise stated, alkyl substituted with (2m'+1) halogen atoms, where m' is the total number of carbon atoms in the alkyl group. For example the term "perhalo(C1-C4)alkyl" is meant to include trifluoromethyl, pentachloroethyl, 1,1,1-trifluoro-2-bromo-2-chloroethyl and the like.

[060] The term "acyl" refers to those groups derived from an organic acid by removal of the hydroxy portion of the acid. Accordingly, acyl is meant to include, for example, acetyl, propionyl, butyryl, decanoyl, pivaloyl, benzoyl and the like.

[061] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. Non-limiting examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl and 1,2,3,4-tetrahydronaphthalene.

[062] The term heteroaryl," refers to aryl groups (or rings) that contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized and the nitrogen heteroatom are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of heteroaryl groups include 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl and 6-quinolyl.

[063] For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

[064] Each of the above terms (e.g., "alkyl," "heteroalkyl," "aryl" and "heteroaryl") is meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[065] Substituents for the alkyl and heteroalkyl radicals (as well as those groups referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R", -SR', halogen, -SiR'R"R'", -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", -NR'-SO_2NR'", -NR"CO_2R', -NH-C(NH_2)=NH, -NR'C(NH_2)=NH, -NH-C(NH_2)=NR', -S(O)R', -SO_2R', -SO_2NR'R", -NR"SO_2R, -CN and -NO_2, in a number ranging from zero to three, with those groups having zero, one or two substituents being particularly preferred. R', R" and R'" each independently refer to hydrogen, unsubstituted (C1-C8)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with one to three halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C1-C4)alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. Typically, an alkyl or heteroalkyl group will have from zero to three substituents, with those groups having two or fewer substituents being preferred in the invention. More preferably, an alkyl or heteroalkyl radical will be unsubstituted or monosubstituted. Most

preferably, an alkyl or heteroalkyl radical will be unsubstituted. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as trihaloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$).

[066] Preferred substituents for the alkyl and heteroalkyl radicals are selected from: -OR', =O, -NR'R", -SR', halogen, -SiR'R"R'", -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', $-NR"CO_2R'$, -NR'-SO_2NR"R'", -S(O)R', -SO2R', $-SO_2$NR'R", -NR"SO_2R, -CN and $-NO_2$, where R' and R" are as defined above. Further preferred substituents are selected from: -OR', =O, -NR'R", halogen, -OC(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', $-NR"CO_2R'$, -NR'-SO_2NR"R'", $-SO_2R'$, $-SO_2$NR'R", -NR"SO_2R, -CN and $-NO_2$.

[067] Similarly, substituents for the aryl and heteroaryl groups are varied and selected from: halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, $-NO_2$, $-CO_2R'$, -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -NR"CO2R', -NR'-C(O)NR"R'", -NR'-SO_2NR"R'", -NH-C(NH2)=NH, -NR'C(NH_2)=NH, -NH-C(NH_2)=NR', -S(O)R', $-SO_2R'$, $-SO_2$NR'R", -NR"SO_2R, $-N_3$, $-CH(Ph)_2$, perfluoro(C1-C4)alko- xy and perfluoro(C1-C4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R" and R'" are independently selected from hydrogen, (C1-C8)alkyl and heteroalkyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-(C1-C4)alkyl and (unsubstituted aryl)oxy-(C1-C4)alkyl. When the aryl group is 1,2,3,4-tetrahydronaphthalene, it may be substituted with a substituted or unsubstituted (C3-C7)spirocycloalkyl group. The (C3-C7)spirocycloalkyl group may be substituted in the same manner as defined herein for "cycloalkyl". Typically, an aryl or heteroaryl group will have from zero to three substituents, with those groups having two or fewer substituents being preferred in the invention. In one embodiment of the invention, an aryl or heteroaryl group will be unsubstituted or monosubstituted. In another embodiment, an aryl or heteroaryl group will be unsubstituted.

[068] Preferred substituents for aryl and heteroaryl groups are selected from: halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, $-NO_2$, $-CO_2R'$, -CONR'R", -C(O)R',-OC(O)NR'R", -NR"C(O)R', -S(O)R', $-SO_2R'$, $-SO_2$NR'R", -NR"SO_2R, $-N_3$, $-CH(Ph)_2$, perfluoro(C1-C4)alkoxy and perfluoro(C1-C4)alkyl, where R' and R" are as defined above. Further preferred substituents are selected from: halogen, -OR', -OC(O)R', -NR'R", -R', -CN, $-NO_2$, $-CO_2R'$, -CONR'R", -NR"C(O)R', $-SO_2R'$, $-SO_2$NR'R", -NR"SO_2R, perfluoro(C1-C4)alkoxy and perfluoro(C1-C4)alkyl.

[069] The substituent $-CO_2H$, as used herein, includes bioisosteric replacements therefor; see, e.g., The Practice of Medicinal Chemistry; Wermuth, C. G., Ed.; Academic Press: New York, 1996; p. 203.

[070] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH_2)q-U-, wherein T and U are independently -NH-, -O-, -CH_2- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH2)r-B-, wherein A and B are independently -CH_2-, -O-, -NH-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CH_2)s-X-(CH_2)t- -, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituent R' in -NR'- and -$S(O)_2$NR'- is selected from hydrogen or unsubstituted (C1-C6)alkyl.

[071] Preferred substituents are disclosed herein and exemplified in the tables, structures, examples, and claims, and may be applied across different compounds of the invention, i.e. substituents of any given compound may be combinatorially used with other compounds.

[072] In particular embodiments applicable substituents are independently substituted or unsubstituted heteroatom, substituted or unsubstituted, optionally heteroatom C1-C6 alkyl, substituted or unsubstituted, optionally heteroatom C2-C6 alkenyl, substituted or unsubstituted, optionally heteroatom C2-C6 alkynyl, or substituted or unsubstituted, optionally heteroatom C6-C14 aryl, wherein each heteroatom is independently oxygen, phosphorus, sulfur or nitrogen.

[073] In more particular embodiments, applicable substituents are independently aldehyde, aldimine, alkanoyloxy, alkoxy, alkoxycarbonyl, alkyloxy, alkyl, amine, azo, halogens, carbamoyl, carbonyl, carboxamido, carboxyl, cyanyl, ester, halo, haloformyl, hydroperoxyl, hydroxyl, imine, isocyanide, iscyante, N-tert-butoxycarbonyl, nitrate, nitrile, nitrite, nitro, nitroso, phosphate, phosphono, sulfide, sulfonyl, sulfo, sulfhydryl, thiol, thiocyanyl, trifluoromethyl or trifluromethyl ether (OCF3).

[074] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the invention contain relatively basic functionalities, acid

addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, oxalic, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. Certain specific compounds of the invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[075] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the invention.

[076] In addition to salt forms, the invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that undergo chemical changes under physiological conditions to provide the compounds of the invention. Additionally, prodrugs can be converted to the compounds of the invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be more bioavailable by oral administration than the parent drug. The prodrug may also have improved solubility in pharmacological compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound of the invention which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound of the invention.

[077] Certain compounds of the invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated

forms and are intended to be encompassed within the scope of the invention. Certain compounds of the invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the invention and are intended to be within the scope of the invention.

[078] Some of the subject compounds possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and specifically designated or depicted chirality is preferred and in many cases critical for optimal activity; however all such isomers are all intended to be encompassed within the scope of the invention.

[079] The compounds of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention.

[080] The term "therapeutically effective amount" refers to the amount of the subject compound that will elicit, to some significant extent, the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician, such as when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated. The therapeutically effective amount will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[081] The invention also provides pharmaceutical compositions comprising the subject compounds and a pharmaceutically acceptable excipient, particularly such compositions comprising a unit dosage of the subject compounds, particularly such compositions copackaged with instructions describing use of the composition to treat an applicable disease or condition (herein).

[082] The compositions for administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules, losenges or the like in the case of solid compositions. In such compositions, the compound is usually a minor component (from about 0.1 to about 50% by weight or preferably

from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[083] Suitable excipients or carriers and methods for preparing administrable compositions are known or apparent to those skilled in the art and are described in more detail in such publications as *Remington's Pharmaceutical Science*, Mack Publishing Co, NJ (1991). In addition, the compounds may be advantageously used in conjunction with other therapeutic agents as described herein or otherwise known in the art, particularly other anti-diabetes or anti-obesity agents. Hence the compositions may be administered separately, jointly, or combined in a single dosage unit.

[084] The amount administered depends on the compound formulation, route of administration, etc. and is generally empirically determined in routine trials, and variations will necessarily occur depending on the target, the host, and the route of administration, etc. Generally, the quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1, 3, 10 or 30 to about 30, 100, 300 or 1000 mg, according to the particular application. In a particular embodiment, unit dosage forms are packaged in a multipack adapted for sequential use, such as blisterpack, comprising sheets of at least 6, 9 or 12 unit dosage forms. The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

[085] The compounds can be administered by a variety of methods including, but not limited to, parenteral, topical, oral, or local administration, such as by aerosol or transdermally, for prophylactic and/or therapeutic treatment. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

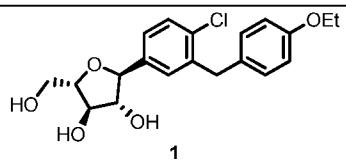
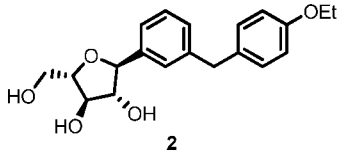
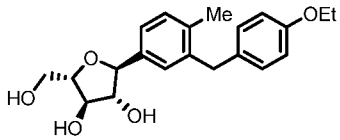
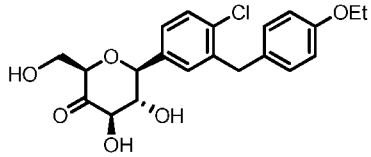
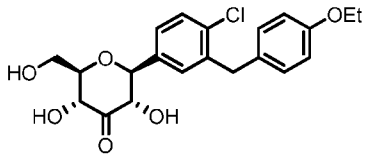
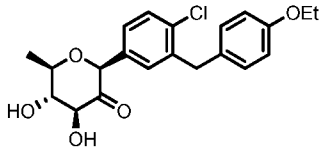
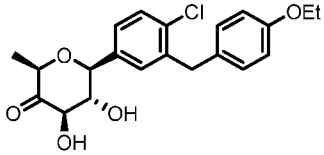
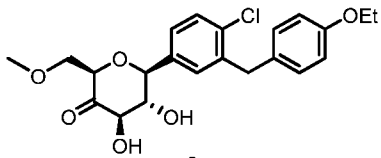
[086] The therapeutics of the invention can be administered in a therapeutically effective dosage and amount, in the process of a therapeutically effective protocol for treatment of the patient. For more potent compounds, microgram (ug) amounts per kilogram of patient may be sufficient, for example, in the range of about 1, 10 or 100 ug/kg to about 0.01, 0.1, 1, 10, or 100 mg/kg of patient weight though optimal dosages are compound specific, and generally empirically determined for each compound.

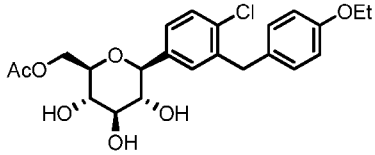
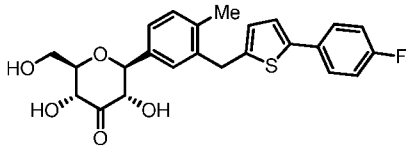
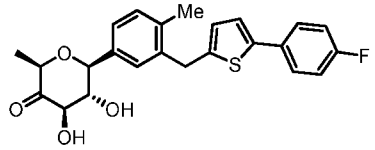
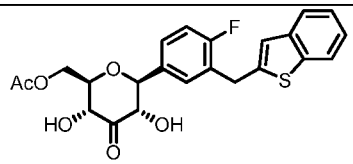
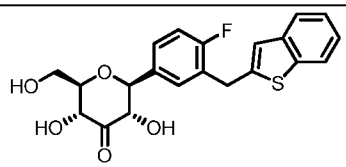
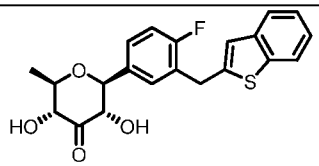
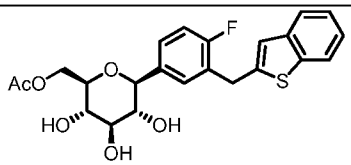
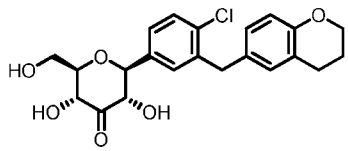
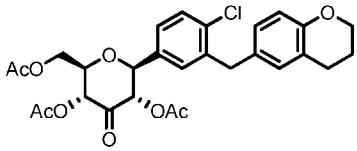
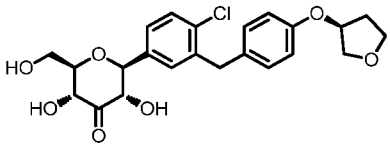
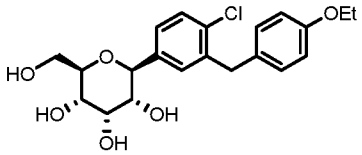
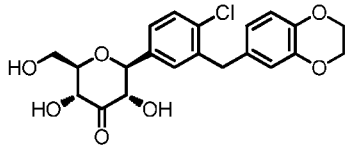
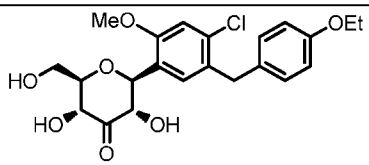
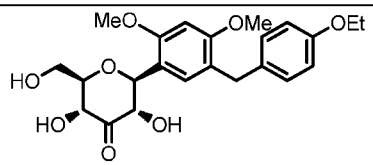
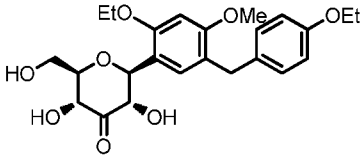
[087] In general, routine experimentation in clinical trials will determine specific ranges for optimal therapeutic effect, for each therapeutic, each administrative protocol, and administration to specific patients will also be adjusted to within effective and safe ranges depending on the patient condition and responsiveness to initial administrations. However, the ultimate administration protocol will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as compounds potency, severity of the disease being treated. For example, a dosage regimen of the compoundss can be oral administration of from 10 mg to 2000 mg/day, preferably 10 to 1000 mg/day, more preferably 50 to 600 mg/day, in two to four (preferably two) divided doses. Intermittent therapy (e.g., one week out of three weeks or three out of four weeks) may also be used.

[088] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein, including citations therein, are hereby incorporated by reference in their entirety for all purposes.

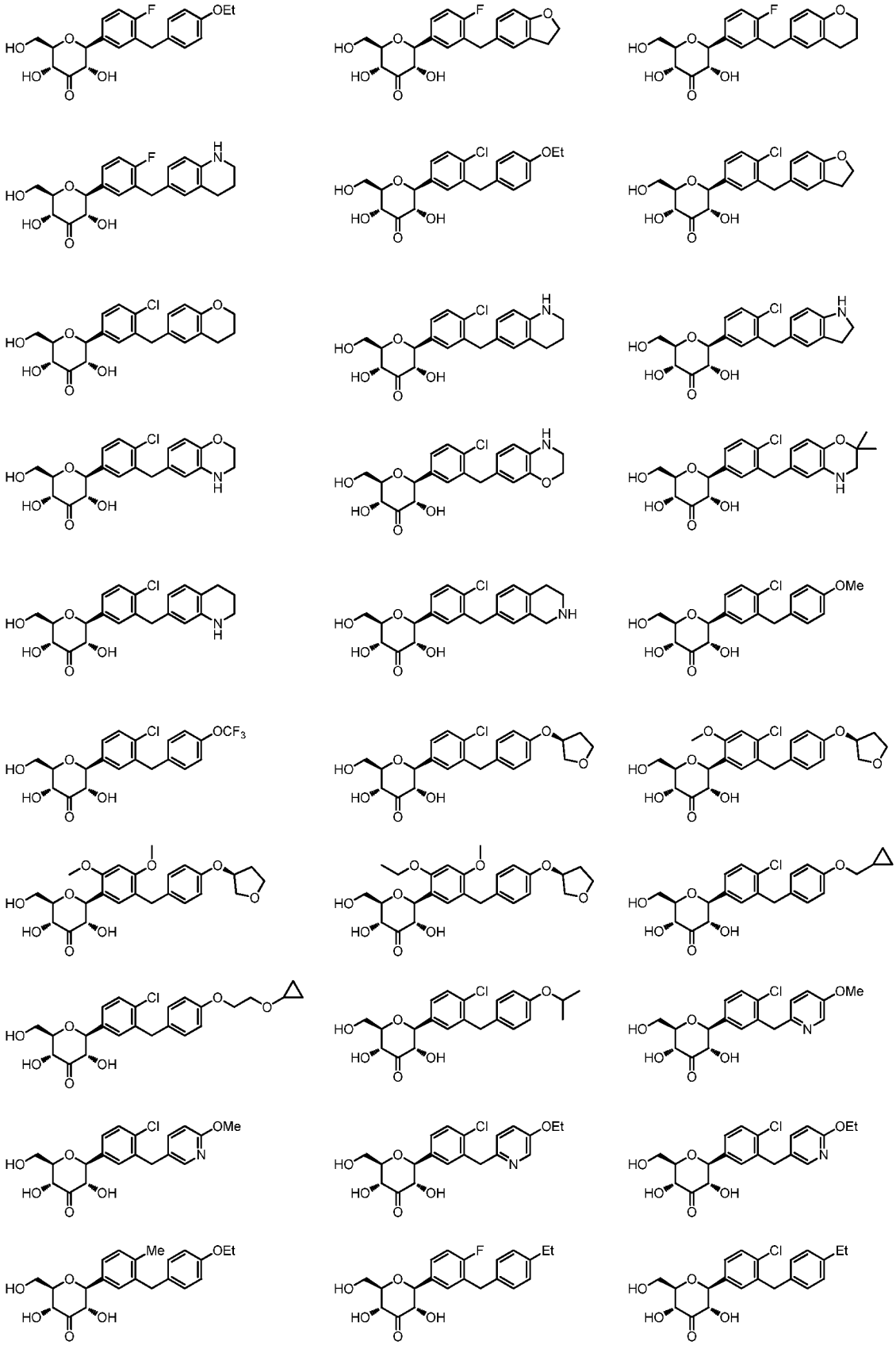
[089] Examples

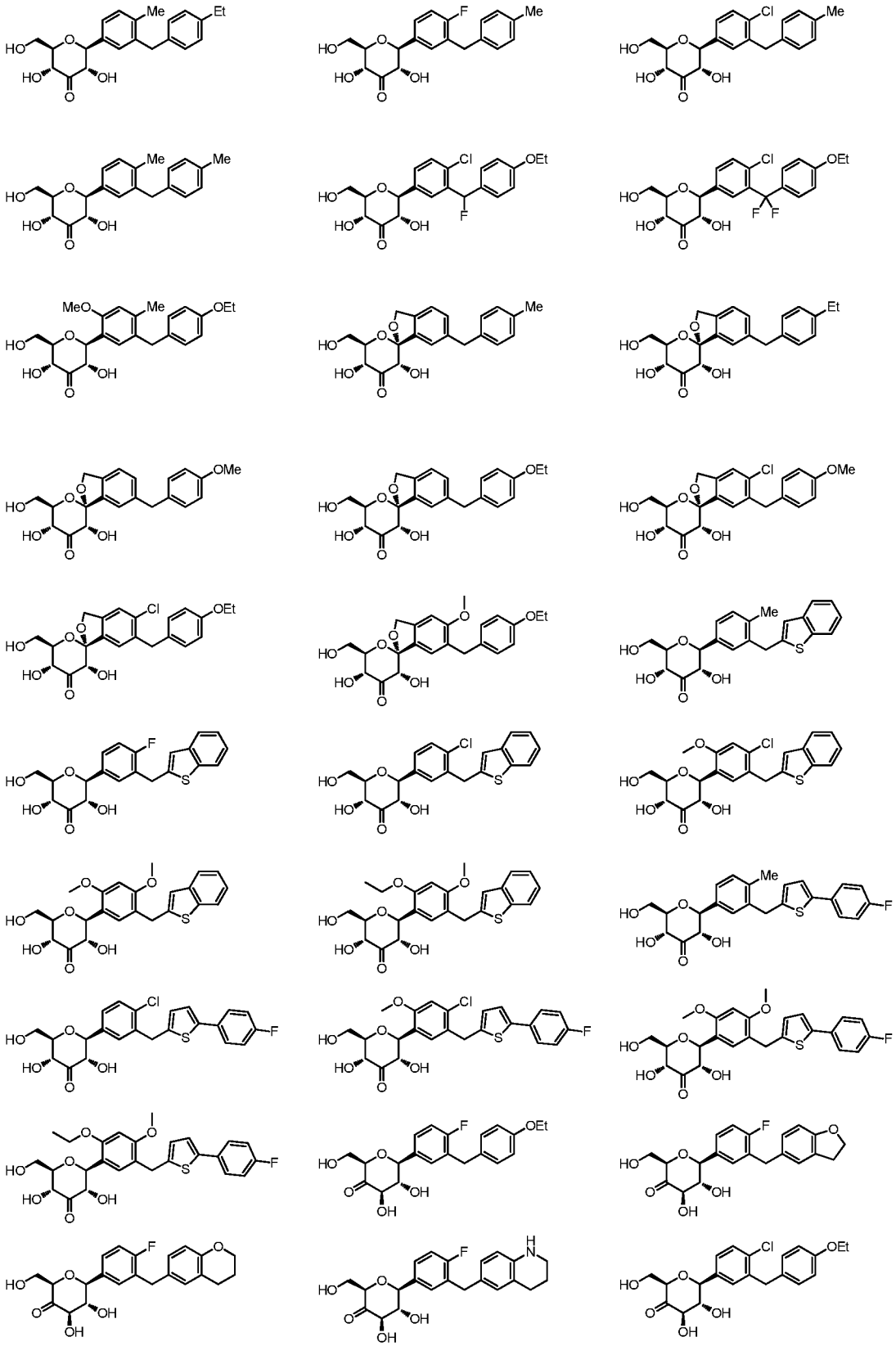
[090] Table A: Exemplary Compounds

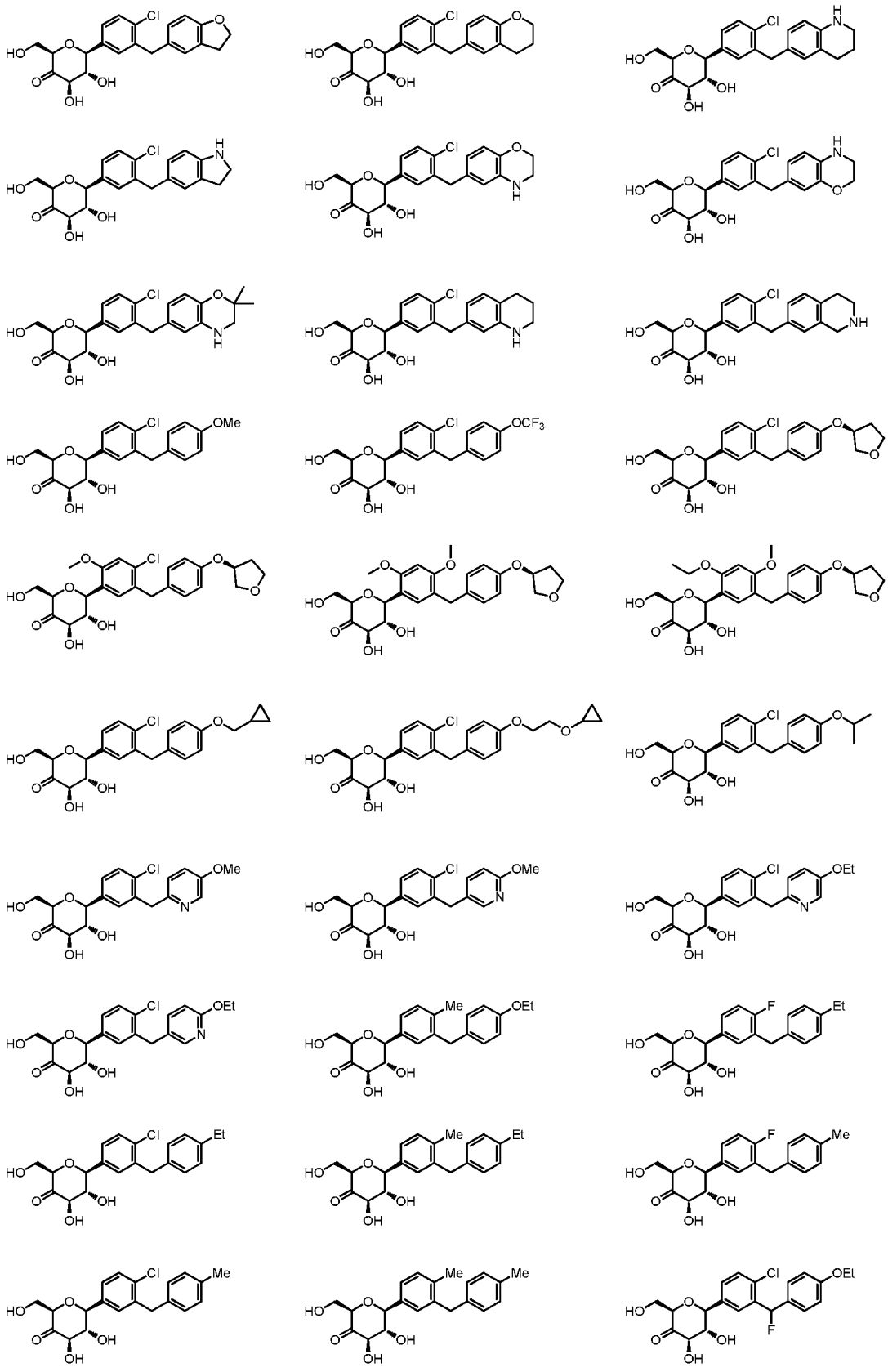
 1	 2
 3	 4
 5	 6
 7	 8

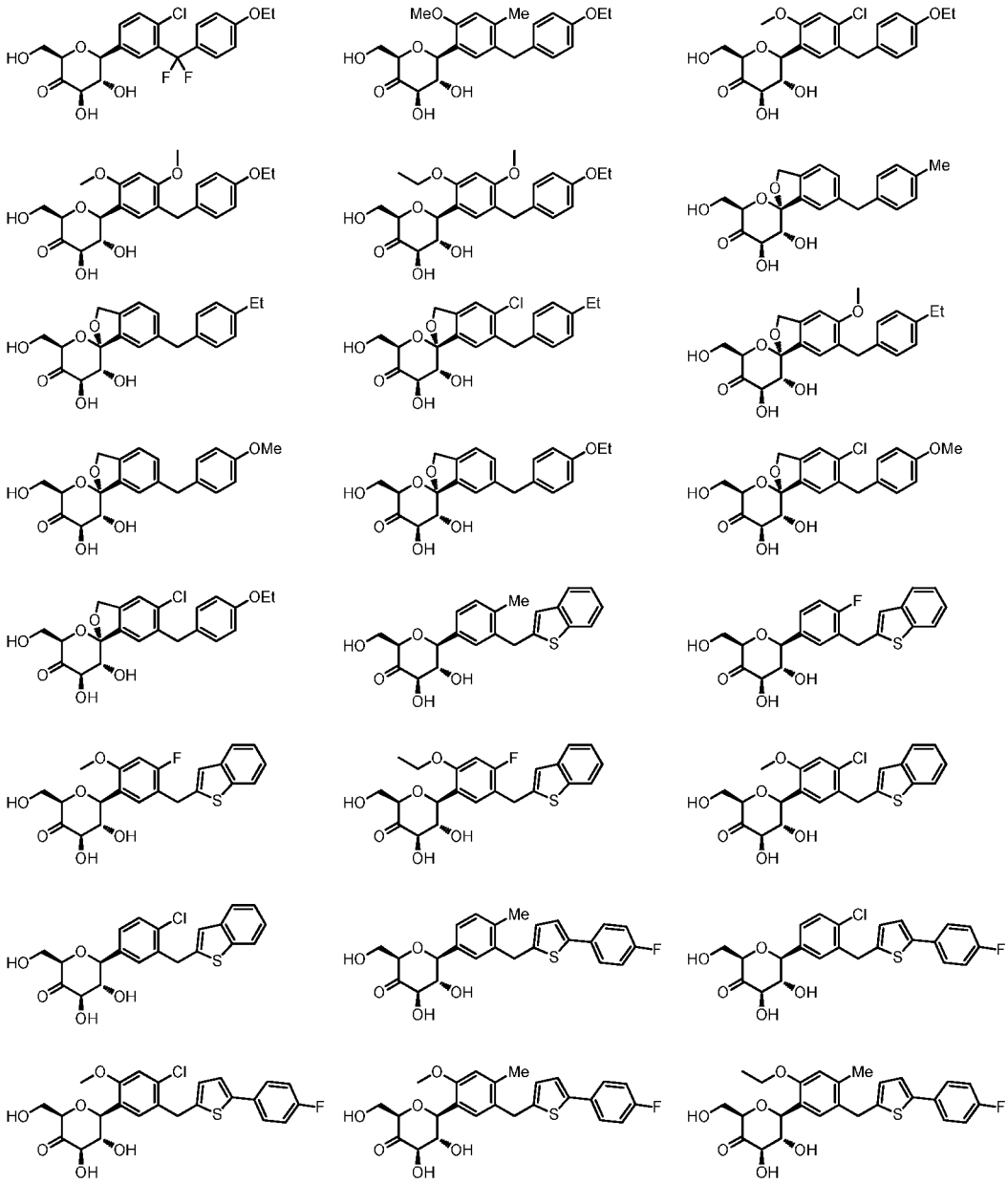
 9	 10
 11	 12
 13	 14
 15	 16
 17	 18
 19	 20
 21	 22
 23	

[091] Table B: Exemplary Compounds: 3-oxo-glucopyranoside and 4-oxo-glucopyranosides:

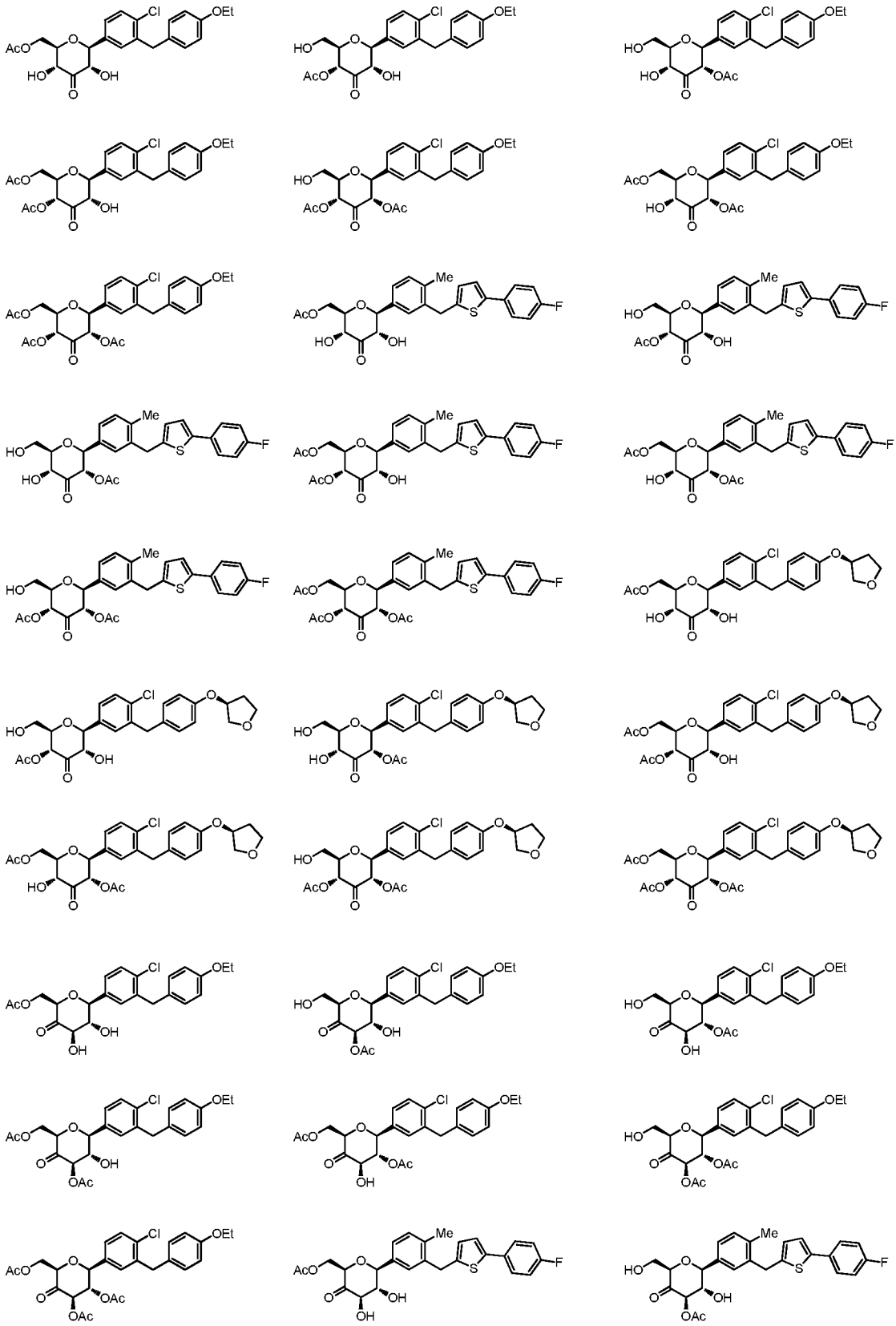


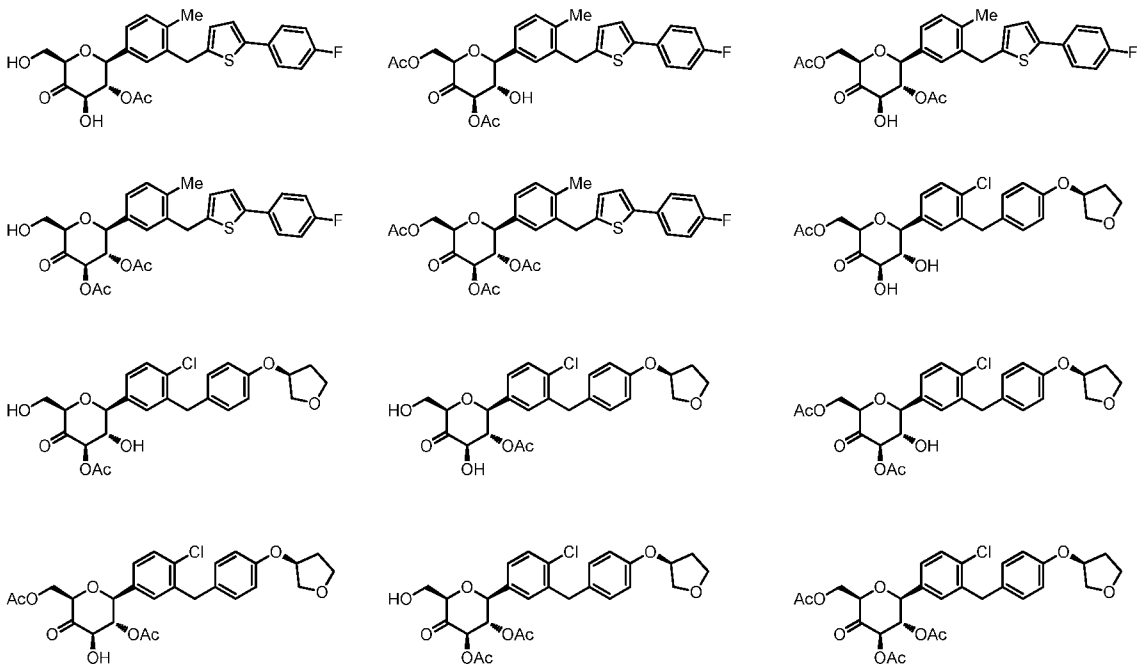




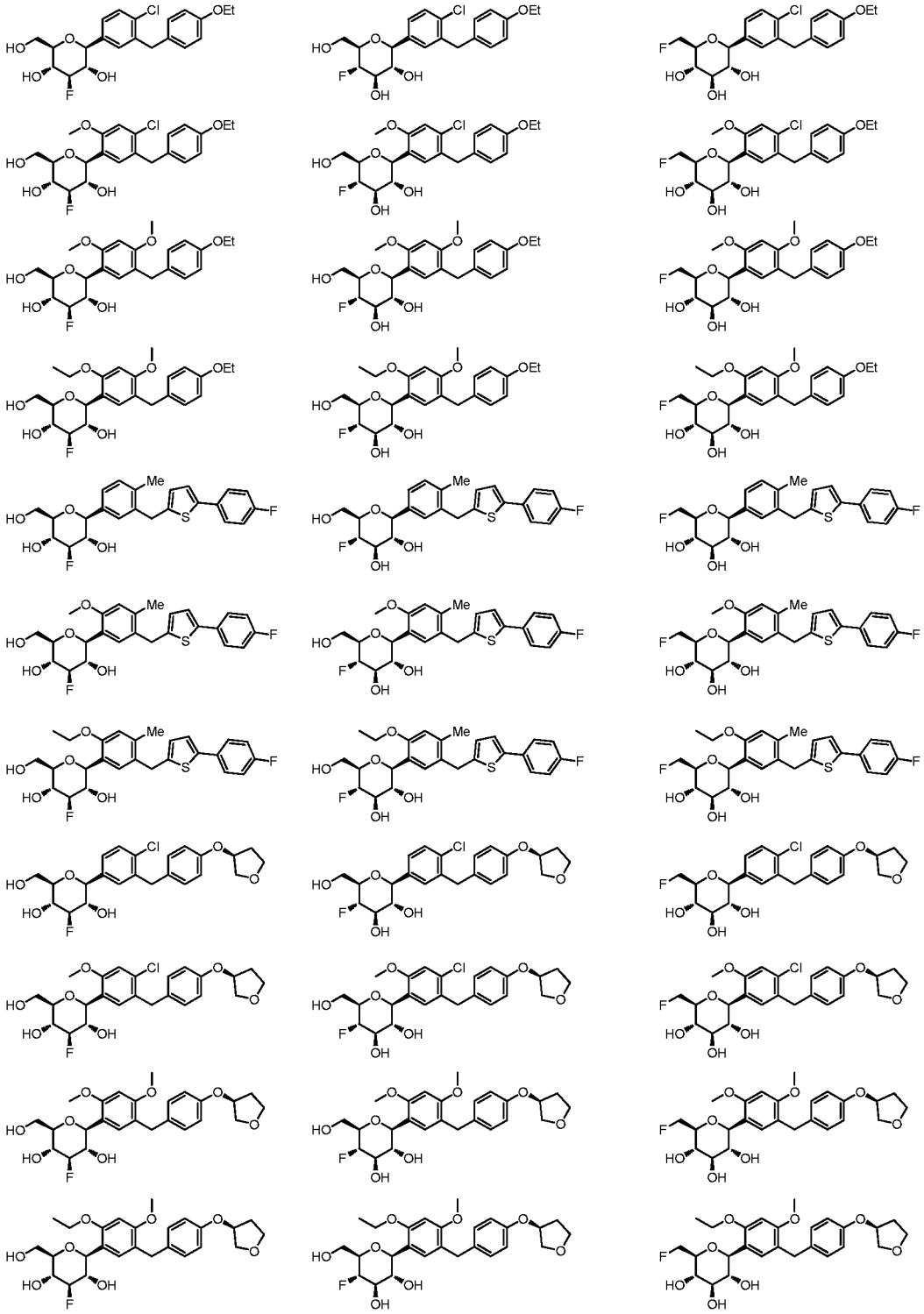


[092] Table C: Additional Exemplary Compounds



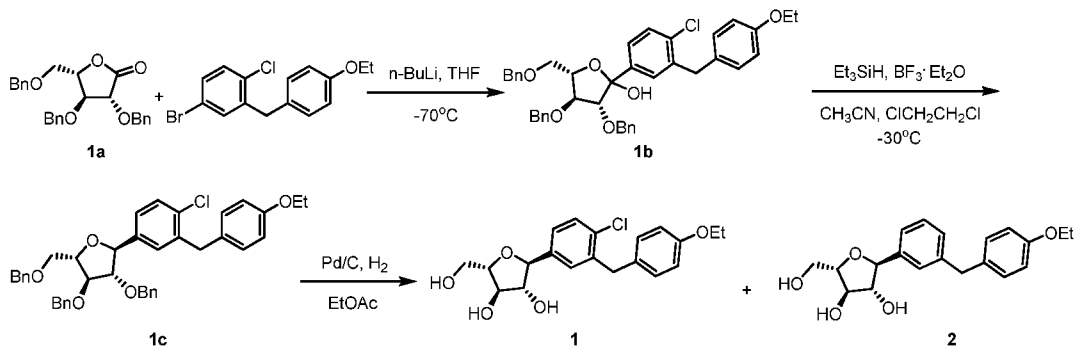


[093] Table D: Additional Exemplary Compounds



[094] **Part I: Synthetic procedures**

[095] Synthesis of (2S,3R,4R,5S)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (1) and (2S,3R,4R,5S)-2-(3-(4-ethoxybenzyl)phenyl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (2)



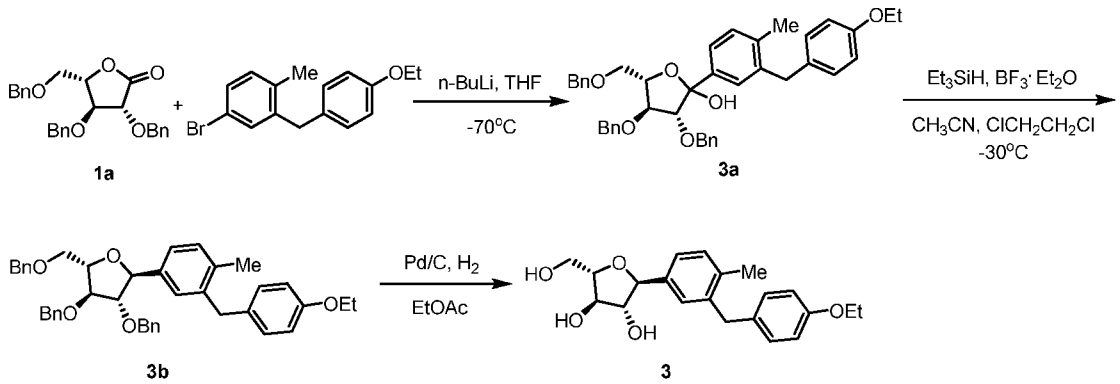
[096] Step 1: (3R,4S,5S)-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydrofuran-2-ol (1b) To a stirred -78°C solution of 5-bromo-2-chloro-4'-ethoxydiphenylmethane (0.64 g, 1.54 mmol) in THF (5 mL) under N_2 was added *n*-BuLi (0.77 mL, 2.4 M, 1.84 mmol) dropwise while keeping the temperature below -70°C. After 30 min, a solution of lactone **1a** (500 mg, 1.54 mmol) in THF (10 mL) was added to the above solution and the mixture was stirred at -78°C for another 2 h. the reaction mixture was quenched by adding saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 5 mL), combine the organic layer, dried and concentrated, the resulting residue was purified by flash column chromatography (silica gel, EtOAc: PE = 1: 6) to give 0.56 g of lactol **1b** as colorless oil, yield: 55%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 2.0 Hz, 1H), 7.45-7.43 (m, 1H), 7.37-7.24 (m, 14H), 7.10-7.08 (m, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.85-6.82 (m, 1H), 6.80-6.73 (m, 2H), 4.67-4.44 (m, 6H), 4.35-4.29 (m, 2H), 4.14-3.93 (m, 6H), 3.67-3.60 (m, 1H), 3.54 (dd, J = 3.6, 10.4 Hz, 1H), 1.39 (t, J = 7.2 Hz, 3H).

[097] Step 2: (2S,3S,4S,5S)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydrofuran (1c) To a cold -30°C solution of the lactol **1b** (0.56 g, 0.84 mmol) in CH_3CN and $ClCH_2CH_2Cl$ (1: 1, 15 mL) was added Et_3SiH (0.27 mL, 1.68 mmol) and $BF_3{\cdot}Et_2O$ (0.31 mL, 1.18 mmol) and stirred for 4.5 h. the reaction mixture was quenched by adding saturated NH_4Cl and extracted with CH_2Cl_2 (3 × 5 mL). Combine the organic layer, dried and concentrated, the resulting residue was purified by flash column chromatography (silica gel, EtOAc: PE = 1:10) to give 0.38 g of **1c** as a colorless oil, yield: 69%.

[098] Step 3: (2S,3R,4R,5S)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (1) and (2S,3R,4R,5S)-2-(3-(4-ethoxybenzyl)phenyl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (2) 10% Pd/C (38 mg) was added to a solution of compound **1c** (0.38 g, 0.58 mmol) in EtOAc (10 mL). After the

resulting suspension was stirred under an atmosphere of H_2 at room temperature for 2 h. the system was bubbled with N_2, and the Pd/C was filtered off. The solution was concentrated under vacuo and purified by Prep-HPLC to give 124 mg of **1** and **2**, total yield: 42%. Compound **1:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.22 (m, 1H), 7.12 (m, 1H), 7.05-6.99 (m, 3H), 6.73 (d, J = 8.8 Hz, 2H), 4.59 (d, J = 6.8 Hz, 1H), 4.33 (br, 3H), 4.16 (t, J = 6.0 Hz, 1H), 3.92-3.86 (m, 6H), 3.72-3.59 (m, 2H), 1.31 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.20, 139.21, 139.61, 131.26, 129.69, 128.35, 124.82, 114.41, 83.24, 83.14, 82.30, 76.79, 63.41, 61.70, 38.28, 14.78; LC-MS (ESI) *m/z*: calcd for [$C_{20}H_{23}ClO_5H^+$], 379.13, found 379.1. compound **2:** ^{1}H NMR (400 MHz, MeOD) δ 7.12 (t, J = 7.6 Hz, 1H), 7.06 (s, 1H), 7.04 (d, J = 8.4 Hz, 3H), 6.95 (d, J = 7.6 Hz, 1H), 6.75 (d, J = 8.4 Hz, 2H), 3.98 (t, J = 6.8 Hz, 1H), 3.96 (q, J = 6.8 Hz, 2H), 3.81 (s, 2H), 3.74 (dd, J = 3.6, 11.2 Hz, 1H), 3.65-3.60 (m, 1H), 3.53 (dd, J = 6.0, 10.8 Hz, 1H), 2.78 (d, J = 7.6 Hz, 2H), 1.31 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, MeOD) δ 158.70, 143.15, 140.59, 131.07, 130.78, 129.32, 128.15, 127.58, 115.37, 73.37, 73.08, 72.73, 65.17, 64.38, 41.94, 41.14, 15.22.

[0103] Synthesis of (2S,3R,4R,5S)-2-(3-(4-ethoxybenzyl)-4-methylphenyl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (3)



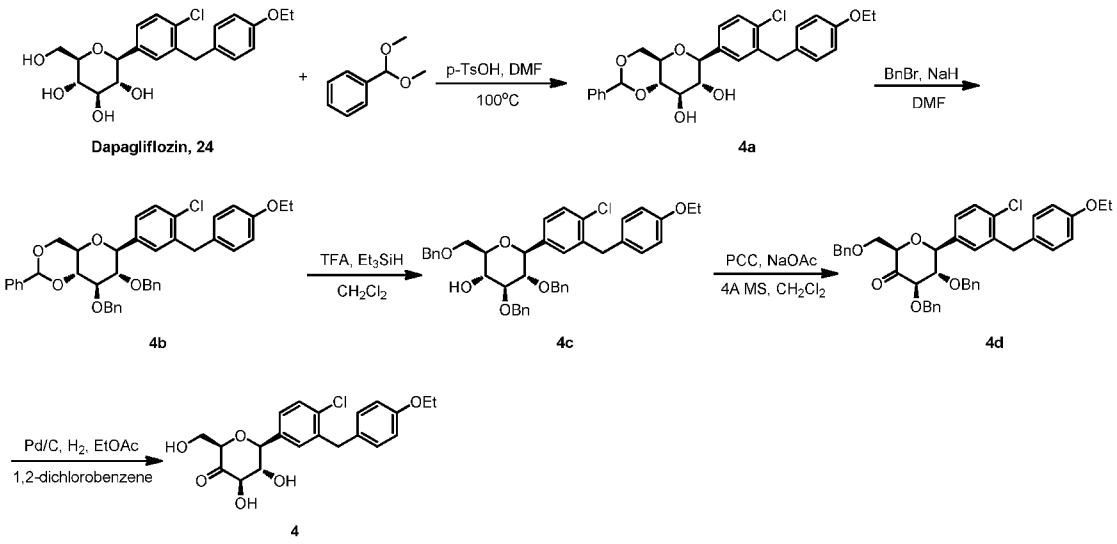
[0104] Step 1: **(3R,4S,5S)-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-2-(3-(4-ethoxybenzyl)-4-methylphenyl)tetrahydrofuran-2-ol** (**3a**) Treatment of lactone **1a** (0.5 g, 1.64 mmol) as described above for the conversion of **1a** to **1b**, afforded 0.79 g of **3a** as colorless oil, yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 2H), 7.36-7.24 (m, 15 H), 7.15-7.14 (m, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.31 (s, 1H), 5.04 (s, 2H), 4.69 (s, 2H), 4.53 (s, 2H), 4.41 (s, 2H), 4.33 (s, 2H), 4.32 (s, 1H), 3.98-3.92 (m, 5H), 3.71-3.68 (m, 1H), 3.59-3.56 (m, 1H), 2.20 (s, 3H), 1.38 (t, J = 6.8 Hz, 3H).

[0105] Step 2: **(2S,3S,4S,5S)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(3-(4-ethoxybenzyl)-4-methylphenyl)tetrahydrofuran** (**3b**) Treatment of lactol **3a** (0.79 g, 1.19 mmol) as described above for the reduction of **1b** to **1c**, afforded 0.62 g of **3b** as colorless oil,

yield: 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.11 (m, 18 H), 6.99 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 4.61-4.57 (m, 2H), 4.54-4.52 (m, 2H), 4.42-4.34 (m, 3H), 4.19 (t, J = 4.4 Hz, 1H), 4.14-4.11 (m, 1H), 4.06-4.01 (m, 1H), 3.99-3.93 (m, 2H), 3.90 (s, 2H), 3.66 (dd, J = 2.0, 5.6 Hz, 1H), 2.21 (s, 3H), 1.38 (t, J = 6.8 Hz, 3H).

[0106] Step 3: **(2S,3R,4R,5S)-2-(3-(4-ethoxybenzyl)-4-methylphenyl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (3)** Treatment of **3b** (0.62 g, 0.99 mmol) as described above for the deprotection of **1c** to **1**, gave 0.16 g of **3** as white syrup, yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07-7.02 (m, 3H), 6.92 (d, J = 8.0 Hz, 2H), 6.72 (d, J = 8.0 Hz, 2H), 4.65 (m, 1H), 4.19 (m, 3H), 4.04 (m, 1H), 3.96 (m, 1H), 3.92 (q, J = 6.8 Hz, 2H), 3.81 (s, 2H), 3.73-3.66 (m, 2H), 2.11 (s, 3H), 1.32 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.01, 139.51, 137.25, 136.54, 132.02, 130.59, 129.42, 127.56, 123.84, 114.30, 83.85, 83.32, 83.29, 82.34, 63.33, 61.91, 38.63, 19.35, 14.82; LC-MS (ESI) *m/z*: calcd for [$C_{21}H_{26}O_5NH_4^+$], 376.21, found 376.10.

[0107] Synthesis of (2R,4R,5R,6S)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-4,5-dihydroxy-2-(hydroxymethyl)dihydro-2H-pyran-3(4H)-one (4)



Step 1: **(4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diol (4a)** To a mixture of **dapagliflozin, 24** (1.05 g, 2.57 mmol), benzaldehyde dimethyl acetal (0.58 mL, 3.86 mmol), and catalytic *p*-toluenesulfonic acid (49 mg, 0.26 mmol) was added anhydrous DMF (15 mL), which was stirred at 100°C under N_2 overnight. Concentrated the solvent and purified by flash column chromatography (silica gel, EtOAc: PE = 1: 5 ~ 1:1), 1.21 g of **4a** was obtained as a white solid, yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.51 (m, 2H), 7.37-7.35 (m, 4H), 7.21-7.17 (m, 2H), 7.12 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.51 (s, 1H), 4.32-4.29 (m, 1H), 4.13-

3.96 (m, 5H), 3.76-3.68 (m, 2H), 3.55-3.43 (m, 3H), 1.40 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.88, 157.40, 139.00, 137.17, 137.13, 134.11, 131.14, 130.40, 129.85, 129.56, 129.23, 128.33, 126.49, 126.39, 114.48, 101.76, 81.77, 80.92, 75.46, 74.77, 70.69, 68.77, 63.37, 38.42, 14.89; LC-MS (ESI) *m/z*: calcd for [$C_{28}H_{29}ClO_6H^+$], 497.17, found 497.4.

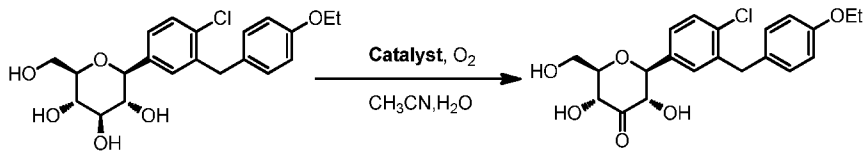
[0108] Step 2: **(4aR,6S,7S,8R,8aR)-7,8-bis(benzyloxy)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine (4b)** At 0°C, to a suspension of NaH (48 mg, 1.19 mmol) in anhydrous DMF (5 mL) was added **4a** (0.27 g, 0.54 mmol), after stirred for 30 min, BnBr (0.20 g, 0.14 mL) was added to the above mixture, the reaction was continued for another 2 h, then quenched by adding saturated aq. NH_4Cl (5 mL), concentrated, then dissolved in ethyl acetate (10 mL), the organic layer was separated and aqueous layer was extracted by ethyl acetate (3 × 10 mL). Combine the organic phase, dried and concentrated. The residue was purified by flash column chromatography (silica gel, EtOAc: PE = 1:5 ~ 1: 1) to give 0.27 g of **4b** as a white solid, yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.57 (m, 2H), 7.47-7.40 (m, 6H), 7.37-7.32 (m, 3H), 7.30-7.24 (m, 5H), 7.11 (d, J = 8.4 Hz, 2H), 6.97 (dd, J = 1.6, 7.2 Hz, 2H), 6.83-6.81 (m, 2H), 5.68 (s, 1H), 5.07 (d, J = 11.2 Hz, 1H), 4.89 (d, J = 11.2 Hz, 1H), 4.58 (d, J = 10.8 Hz, 1H), 4.43 (q, J = 5.2 Hz, 1H), 4.34 (d, J = 9.2 Hz, 1H), 4.14 (d, J = 15.6 Hz, 1H), 4.04-3.94 (m, 5H), 3.88-3.80 (m, 2H), 3.62 (q, J = 4.8 Hz, 1H), 3.59-3.54 (m, 1H), 1.43 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.47, 139.14, 138.53, 137.61, 137.57, 137.43, 134.18, 131.14, 130.52, 129.85, 129.64, 129.00, 128.43, 128.31, 128.26, 128.11, 128.08, 127.76, 127.71, 126.62, 126.05, 114.53, 101.17, 83.25, 82.84, 82.37, 81.83, 75.35, 75.23, 70.80, 68.95, 63.36, 38.37, 14.95; LC-MS (ESI) *m/z*: calcd for [$C_{42}H_{41}ClO_6H^+$], 677.27, found 677.60.

[0109] Step 3: **(2R,3R,4S,5S,6S)-4,5-bis(benzyloxy)-2-(benzyloxymethyl)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran-3-ol (4c)** TFA (0.15 mL, 1.92 mmol) was added dropwise to a solution of **4b** (0.26 g, 0.38 mmol) and Et_3N (0.3 mL, 1.92 mmol) in CH_2Cl_2 (5 mL) at 0°C. When the addition was complete, the reaction was warmed to room temperature for 2 h. The mixture was diluted with EtOAc and washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated to produce a residue, which was purified by flash column chromatography (silica gel, EtOAc: PE = 1:15~1:5) to give 0.22 g of **4c** as a light yellow oil, yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4-7.41 (m, 3H), 7.39-7.34 (m, 8H), 7.29-7.26 (m, 5H), 7.10 (d, J = 8.8 Hz, 2H), 7.00-6.96 (m, 2H), 6.80 (d, J = 8.8 Hz, 2H), 5.00-4.96 (m, 2H), 4.90 (d, J = 11.2 Hz, 1H), 4.67-4.58 (m, 1H), 4.47 (t, J = 10.8 Hz, 1H), 4.27-4.23 (m, 1H), 4.20-4.12 (m, 1H), 4.04-3.98 (m, 3H), 3.95-3.78 (m, 4H), 3.76-3.59 (m, 2H), 3.52-3.45 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H); LC-MS (ESI) *m/z*: calcd for [$C_{42}H_{43}ClO_6NH_4^+$], 696.31, found 696.67.

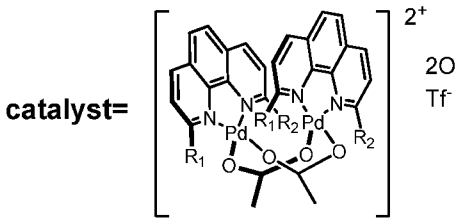
[0110] Step 4: **(2R,4R,5S,6S)-4,5-bis(benzyloxy)-2-(benzyloxymethyl)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)dihydro-2H-pyran-3(4H)-one (4d)** A mixture of compound **4c 4c** (0.22 g, 0.32 mmol) (0.19 g, 0.38 mmol), PCC (0.33 g, 1.52 mmol), sodium acetate (0.21 g, 1.52 mmol), and 4A activated molecular sieves (0.55 g) was placed in a light protected flask under Ar, and then anhydrous CH_2Cl_2 (20 mL) was added, after 2 h, the reaction mixture was diluted with CH_2Cl_2, silica gel was added, and the mixture was evaporated to dryness. The resulting residue was purified by flash column chromatography (silica gel, EtOAc: PE = 1:10 ~ 1: 5) to give 0.2 g of **4d** as a colorless syrup (~ 60% HPLC purity).

[0111] Step 5: **(2R,4R,5R,6S)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-4,5-dihydroxy-2-(hydroxymethyl)dihydro-2H-pyran-3(4H)-one (4)** To a solution of **4d** (0.2 g, ~60% HPLC purity), 1,2-dichlorobenzene (0.22 g, 1.48 mmol) in EtOAc (15 mL) was added Pd/C (10 wt%; 20 mg) and the mixture was stirred at rt for 3 h under H_2. The reaction mixture was filtered through celite and the filtrate was concentrated to produce a residue, which was purified by Pre-TLC (MeOH: CH_2Cl_2 = 1: 15) to give 4 mg of **4** as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 1H), 7.27 (dd, J = 2.0, 8.4 Hz, 1H), 7.20 (d, J = 2.0 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 4.48 (d, J = 9.6 Hz, 1H), 4.26 (d, J = 9.6 Hz, 1H), 4.18 (d, J = 9.6 Hz, 1H), 4.11-3.98 (m, 5H), 3.91 (dd, J = 4.4, 12.4 Hz, 1H), 3.52-3.48 (m, 1H), 1.40 (t, J = 7.2 Hz, 3H); LC-MS (ESI) *m/z*: calcd for $[C_{21}H_{23}ClO_6NH_4^+]$, 424.15, found 424.33.

[0112] Synthesis of (2S,3S,5R,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-3,5-dihydroxy-6-(hydroxymethyl)dihydro-2H-pyran-4(3H)-one (5)



dapagliflozin, 24 5



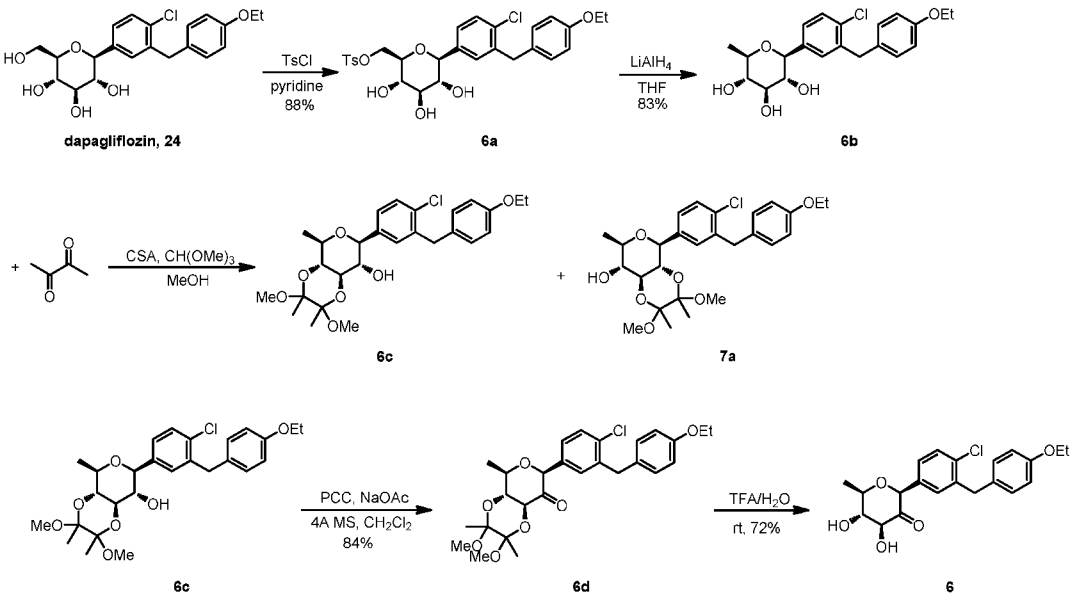
catalyst A: R_1=R_2=Me
catalyst B: R_1=H,R_2=Me
catalyst C: R_1=H,R_2=OMe

[0113] Dapagliflozin, 24 (1.8 g, 4.40 mmol) was dissolved in CH_3CN/H_2O (30 mL, 10:1). Then **catalyst A (B, or C)** (230 mg, 5mol %) was added, and the mixture was stirred at room temperature for 2 days. LC-MS showed the reaction to be completed. After evaporation of the

solvents, the residue was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2 = 1:100 ~ 1:50) to give 0.92 g of the **5** as a white solid, yield: 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 1H), 7.27 (dd, J = 2.0, 8.0 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 4.48 (d, J = 9.6 Hz, 1H), 4.26 (d, J = 9.6 Hz, 1H), 4.19 (d, J = 9.6 Hz, 1H), 4.15-4.09 (m, 1H), 4.07-3.97 (m, 4H), 3.92 (dd, J = 4.4, 12.4 Hz, 1H), 3.51-3.47 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.41, 157.46, 156.90, 139.37, 136.11, 134.77, 130.96, 129.86, 129.76, 129.70, 125.93, 115.73, 114.47, 84.29, 83.18, 77.05, 72.73, 63.39, 62.50, 38.36, 14.84; LC-MS (ESI) *m/z*: calcd for [$C_{21}H_{23}ClO_6NH_4^+$], 424.15, found 424.6.

[0114] Synthesis of (2S,4S,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-4,5-dihydroxy-6-methyldihydro-2H-pyran-3(4H)-one (6)

[0115]



[0116] Step 1: ((2R,3S,4R,5R,6S)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)methyl 4-methylbenzenesulfonate (6a) At 0°C, to a well stirred solution of **dapagliflozin, 24** (0.54 g, 1.32 mmol) in anhydrous pyridine (10 mL) was added p-toluenesulfonyl chloride (0.63 g, 3.3 mmol). The obtained system was stirred for another 2h. The reaction was quenched with H_2O, and then concentrated the pyridine under vacuo. The obtained residue was dissolved in EtOAc (15 mL) and 1N HCl (5 mL), separated the organic layer, and the water layer was extracted with EtOAc (3 × 10 mL), combined the organic phase and concentrated. Purification by flash column chromatography (silica gel, EtOAc: PE = 1:1 ~ EtOAc) gave 0.65 g of the **6a** as colorless oil, yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.68 (m, 2H), 7.31-7.26 (m, 2H), 7.22-7.17 (m, 3H), 7.13 (dd, J = 1.6, 8.0 Hz, 1H), 7.06-7.04 (m, 2H), 6.78-6.75 (m, 2H), 4.36 (dd, J = 4.4, 11.2 Hz, 1H), 4.21 (d, J = 9.6 Hz, 1H), 4.04-

3.99 (m, 2H), 3.96-3.91 (m, 3H), 3.65 (t, J = 9.2 Hz, 1H), 3.58 (t, J = 9.2 Hz, 1H), 3.52-3.49 (m, 1H), 3.38 (t, J = 9.2 Hz, 1H), 3.20 (br, 3H), 2.37 (s, 3H), 1.35 (t, J = 6.8 Hz, 3H); LC-MS (ESI) *m/z*: calcd for [$C_{28}H_{31}ClO_8SNH_4^+$], 580.18, found 580.4.

[0117] Step 2: **(2S,3R,4S,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-methyltetrahydro-2H-pyran-3,4,5-triol (6b)** At 0°C, to a stirred solution of **6a** (0.33 g, 0.59mmol) in anhydrous THF (15 mL) was added $LiAlH_4$ (89 mg, 2.36 mmol) dropwise. After stirring for 30 min., the whole system was heated to 65°C for another 2 h. then the reaction was cooled to 0°C, and 1N HCl was added to quench the reaction, separated the organic layer, and the water layer was extracted with EtOAc (3 × 5 mL), combined the organic layer, and concentrated under vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc: PE = 1:1 ~ EtOAc) to give 190 mg of **6b** as colorless oil, yield: 83%。 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 4.29 (br, 3H), 4.05-3.90 (m, 5H), 3.44 (m, 1H), 3.34-3.27 (m, 2H), 3.11 (t, J = 8.0 Hz, 1H), 1.35 (t, J = 6.8 Hz, 3H), 1.25 (d, J = 5.6 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.31, 139.01, 137.23, 134.06, 131.09, 130.34, 129.69, 129.63, 126.68, 114.43, 80.92, 77.92, 75.77, 75.60, 75.12, 63.32, 38.37, 17.92, 14.79; LC-MS (ESI) *m/z*: calcd for [$C_{21}H_{25}ClO_5NH_4^+$], 410.17, found 410.13.

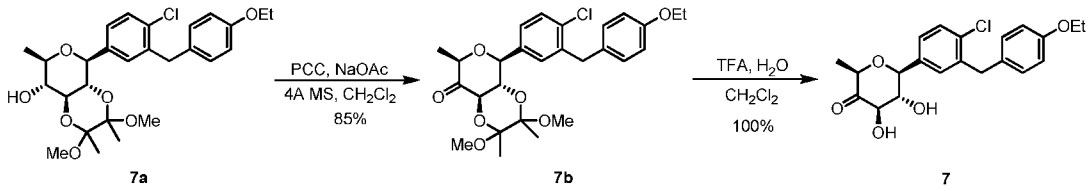
[0118] Step 3: **(4aR,5R,7S,8S,8aR)-7-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3-dimethoxy-2,3,5-trimethylhexahydro-2H-pyrano[4,3-b][1,4]dioxin-8-ol (6c) and (4aS,5S,7R,8R,8aS)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3-dimethoxy-2,3,7-trimethylhexahydro-2H-pyrano[4,3-b][1,4]dioxin-8-ol (7a)** A solution containing **6b** (0.38 g, 0. 97 mmol), 2,3-butanedione (0.42 g, 4.85 mmol, 0.42 mL), trimethylorthoformate (0.41 g, 3.88 mmol), and 10-camphorsulfonic acid (0.12 g, 0.49 mmol) in 20 mL of MeOH was heated at reflux overnight. The cooled reaction mixture was neutralized with NEt_3 and concentrated under diminished pressure. The residue was purified by flash column chromatography (silica gel, EtOAc: PE = 1:10 ~ 1: 5) to give 0.19 g of **6c** and 0.21 g of **7a**. Yield: 82%. **6c**: yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.0 Hz, 1H), 7.21-7.19 (m, 2H), 7.11-7.07 (m, 2H), 6.82-6.79 (m, 2H), 4.14-4.09 (m, 2H), 4.06-3.95 (m, 4H), 3.76 (t, J = 9.6 Hz, 1H), 3.67-3.62 (m, 2H), 3.39 (t, J = 9.6 Hz, 1H), 3.29 (s, 6H), 1.39 (t, J = 6.8 Hz, 3H), 1.33 (s, 3H), 1.29-1.28 (m, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.37, 137.34, 134.16, 131.20, 130.26, 129.83, 129.70, 126.54, 114.45, 99.59, 81.58, 74.11, 73.86, 72.67, 71.22, 63.36, 47.98, 47.83, 38.41, 17.71, 17.67, 16.99, 14.87; LC-MS (ESI) *m/z*: calcd for [$C_{27}H_{35}ClO_7NH_4^+$], 524.24, found 524.19. **7a**: white syrup, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 1H), 7.22-7.20 (m, 2H), 7.07 (d, J = 8.8 Hz, 2H), 6.79-6.76 (m, 2H), 4.32 (d, J = 9.6 Hz, 1H), 4.02-3.96 (m, 4H), 3.75 (t, J = 9.6 Hz, 1H), 3.55-3.42 (m,

3H), 3.31 (s, 3H), 2.65 (s, 3H), 1.40-1.34 (m, 6H), 1.29 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.26, 138.53, 137.16, 133.41, 131.48, 129.76, 129.64, 129.12, 125.98, 114.29, 99.59, 99.50, 78.22, 76.13, 74.29, 72.94, 71.13, 63.28, 47.85, 47.43, 38.18, 17.86, 17.55, 17.44, 14.79; LC-MS (ESI) *m/z*: calcd for [$C_{27}H_{35}ClO_7Na^+$], 529.20, found 529.31.

[0119] Step 4: **(4aR,5R,7S,8aS)-7-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3-dimethoxy-2,3,5-trimethyltetrahydro-2H-pyrano[4,3-b][1,4]dioxin-8(3H)-one (6d)** A mixture of compound **6c** (0.19 g, 0.38 mmol), PCC (0.33 g, 1.52 mmol), sodium acetate (0.21 g, 1.52 mmol), and 4A activated molecular sieves (0.55 g) was placed in a light protected flask under Ar, and then anhydrous CH_2Cl_2 (20 mL) was added, after 2 h, the reaction mixture was diluted with CH_2Cl_2, silica gel was added, and the mixture was evaporated to dryness. The resulting residue was purified by flash column chromatography (silica gel, EtOAc: PE = 1:10 ~ 1: 5) to give 0.16 g of **6d** as a colorless oil, yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.4 Hz, 1H), 7.09-7.01 (m, 4H), 6.82-6.79 (m, 2H), 4.80 (s, 1H), 4.62 (d, J = 10.8 Hz, 1H), 4.04-3.97 (m, 5H), 3.74 (t, J = 9.6 Hz, 1H), 3.29, 3.27 (s, 6H), 1.40-1.34 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.53, 157.33, 156.93, 138.71, 134.43, 132.78, 131.07, 130.89, 129.91, 129.43, 127.30, 114.40, 100.53, 99.59, 73.73, 75.32, 74.32, 73.75, 63.33, 48.49, 47.85, 38.35, 17.61, 17.45, 16.79, 14.85; LC-MS (ESI) *m/z*: calcd for [$C_{27}H_{33}ClO_7NH_4^+$], 522.23, found 522.22.

[0120] Step 5: **(2S,4S,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-4,5-dihydroxy-6-methyldihydro-2H-pyran-3(4H)-one (6)** To a solution containing **6d** (0.16 g, 0.32 mmol) in CH_2Cl_2 (20 mL) was added 10: 1 of TFA-H_2O (4.4 mL), the reaction mixture was stirred at r.t. for 1 h, then separated the organic phase by adding H_2O into the above reaction, the exceed TFA was neutralized with saturated aq. $NaHCO_3$, concentrated the organic phase and purified by flash column chromatography (silica gel, EtOAc: PE = 1:1~ EtOAc) to give 90 mg of **6** as a white solid, yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.4 Hz, 1H), 7.09-7.06 (m, 3H), 7.00 (d, J = 2.0 Hz, 1H), 6.83-6.81 (m, 2H), 4.87 (s, 1H), 4.32 (d, J = 9.2 Hz, 1H), 4.05-4.01 (m, 4H), 3.92 (m, 1H), 3.54 (t, J = 9.6 Hz, 1H), 2.90 (br, 2H), 1.45-1.38 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.17, 157.43, 139.01, 139.01, 134.68, 132.29, 130.98, 130.41, 129.91, 129.56, 126.86, 114.46, 82.04, 80.21, 79.87, 75.69, 63.39, 38.34, 17.55, 14.87; LC-MS (ESI) *m/z*: calcd for [$C_{21}H_{23}ClO_5NH_4^+$], 408.16, found 408.24.

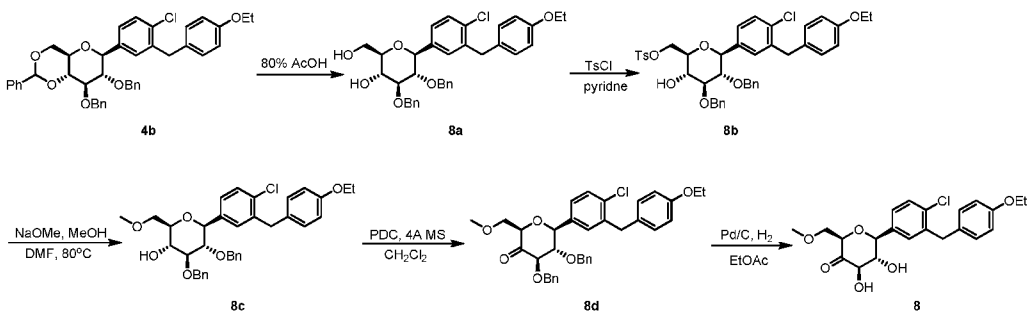
[0121] Synthesis of (2R,4R,5R,6S)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-4,5-dihydroxy-2-methyldihydro-2H-pyran-3(4H)-one (7)



[0122] Step 1: (4aS,5S,7R,8aR)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3-dimethoxy-2,3,7-trimethyltetrahydro-2H-pyrano[4,3-b][1,4]dioxin-8(3H)-one (7b) Treatment of **7a** (0.33 g, 0.65 mmol) as described above for the oxidation of **6c** to **6d**, with purification of the product by flash column chromatography gave 0.28 g of **7b** as white syrup, yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 1H), 7.23-7.21 (m, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 4.66 (d, J = 9.6 Hz, 1H), 4.62 (d, J = 10.4 Hz, 1H), 4.13-4.08 (m, 1H), 4.02-3.93 (m, 4H), 3.80 (t, J = 10.0 Hz, 1H), 3.26 (s, 3H), 2.60 (s, 3H), 1.38-1.31 (m, 9H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.83, 156.95, 138.46, 135.60, 133.41, 130.84, 129.26, 129.22, 128.87, 125.55, 113.94, 100.09, 99.17, 78.02, 76.43, 74.53, 73.43, 62.85, 47.94, 47.05, 37.75, 16.95, 14.39, 13.58; LC-MS (ESI) *m/z*: calcd for [$C_{27}H_{33}ClO_7NH_4^+$], 522.23, found 522.30.

[0123] Step 2: (2R,4R,5R,6S)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-4,5-dihydroxy-2-methyldihydro-2H-pyran-3(4H)-one (7) Treatment of **7b** (0.28 g, 0.55 mmol) as described above for the deprotection of **6d** to **6**, with purification of the product from flash column chromatography gave 0.21 g of **7** as white solid, yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.0 Hz, 1H), 7.24-7.21 (m, 2H), 7.11-7.10 (m, 1H), 7.09-7.08 (m, 1H), 6.84-6.82 (m, 1H), 6.81-6.80 (m, 1H), 4.52 (d, J = 9.2 Hz, 1H), 4.33 (d, J = 9.2 Hz, 1H), 4.21 (q, J = 6.4 Hz, 1H), 4.11-4.07 (m, 1H), 4.03 (q, J = 6.8 Hz, 2H), 3.70 (t, J = 9.2 Hz, 1H), 1.41-1.37 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.54, 157.74, 139.42, 135.89, 134.56, 131.05, 130.03, 129.85, 129.81, 126.23, 114.50, 80.63, 79.38, 79.20, 63.40, 38.37, 14.87, 13.97; LC-MS (ESI) *m/z*: calcd for [$C_{21}H_{23}ClO_5NH_4^+$], 408.16, found 408.4.

[0124] Synthesis of (2R,4R,5R,6S)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-4,5-dihydroxy-2-(methoxymethyl)dihydro-2H-pyran-3(4H)-one (8)



[0125] Step 1: **(2R,3R,4S,5S,6S)-4,5-bis(benzyloxy)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol (8a) 4b** (0.27 g, 0.40 mmol) was dissolved in a mixture of 80% HOAc and CH_2Cl_2 (5: 1, 6 mL), which was stirred at r.t. overnight. Concentrated the solvent and dissolved in EtOAc (10 mL), washed with saturated aq. $NaHCO_3$ (3 mL). The water layer was extracted with EtOAc (3 × 5 mL), combine the organic phase, dried and concentrated. The residue was purified by flash column chromatography (silica gel, EtOAc: PE = 1: 3) to give 0.25 g of **8a** as a white solid, yield: 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.34 (m, 6H), 7.25-7.21 (m, 5H), 7.06 (d, J = 8.4 Hz, 2H), 6.94-6.92 (m, 2H), 6.78 (d, J = 8.8 Hz, 2H), 4.96 (d, J = 11.6 Hz, 1H), 4.82 (d, J = 11.6 Hz, 1H), 4.39 (d, J = 10.4 Hz, 1H), 4.20 (d, J = 9.2 Hz, 1H), 4.10-4.06 (m, 1H), 3.99-3.94 (m, 3H), 3.87-3.82 (m, 2H), 3.78 (dd, J = 4.8, 12.0 Hz, 1H), 3.67 (t, J = 9.2 Hz, 1H), 3.62-3.58 (m, 1H), 3.44-3.39 (m, 2H), 3.17 (br, 2H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.28, 138.98, 138.38, 137.63, 137.36, 133.93, 131.02, 130.82, 130.38, 129.67, 129.48, 128.72, 128.48, 128.14, 127.84, 127.79, 127.76, 127.58, 126.45, 114.38, 85.89, 83.58, 80.91, 79.30, 75.26, 74.63, 70.76, 63.22, 62.50, 38.17, 14.76; LC-MS (ESI) *m/z*: calcd for [$C_{35}H_{37}ClO_6NH_4^+$], 606.26, found 606.5.

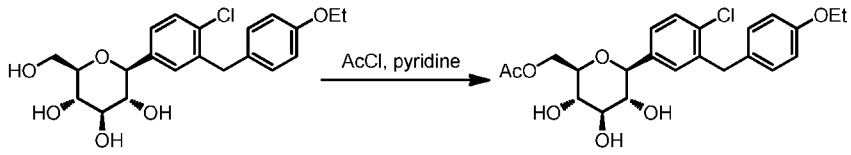
[0126] Step 2: **((2R,3R,4S,5S,6S)-4,5-bis(benzyloxy)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-3-hydroxytetrahydro-2H-pyran-2-yl)methyl 4-methylbenzenesulfonate (8b)** At 0°C, to a well stirred solution of **8a** (0.31 g, 0.53 mmol) in anhydrous pyridine (5 mL) was added *p*-toluenesulfonyl chloride (0.63 g, 3.3 mmol). The obtained system was stirred for another 2h. The reaction was quenched with H_2O, and then concentrated the pyridine under vacuo. The obtained residue was dissolved in EtOAc (10 mL) and 1N HCl (5 mL), separated the organic layer, and the water layer was extracted with EtOAc (3 × 5 mL), combined the organic phase and concentrated. Purification by flash column chromatography (silica gel, EtOAc: PE = 1:5) gave 0.33 g of the **8b** as colorless oil, yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 2H), 7.37-7.29 (m, 6H), 7.25-7.21 (m, 5H), 7.16-7.14 (m, 2H), 7.05 (d, J = 8.8 Hz, 2H), 6.93-6.90 (m, 2H), 6.77 (d, J = 8.8 Hz, 2H), 4.93 (d, J = 11.6 Hz, 1H), 4.74 (d, J = 11.6 Hz, 1H), 4.34-4.26 (m, 3H), 4.11-4.05 (m, 2H), 3.99-3.93 (m, 3H), 3.81 (d, J = 10.4 Hz, 1H), 3.65 (t, J = 9.2 Hz, 1H), 3.55-3.46 (m, 2H), 3.36 (t, J = 9.2 Hz, 1H), 2.39 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.35, 144.71, 138.99, 138.33, 137.35, 137.29, 133.94, 132.77, 131.09, 130.37, 129.72, 129.70, 129.48, 128.61, 128.24, 127.96, 127.88, 127.81, 127.71, 126.40, 114.43, 85.60, 83.50, 80.90, 77.10, 75.33, 74.75, 69.63, 68.95, 63.29, 38.26, 21.59, 14.84; LC-MS (ESI) *m/z*: calcd for [$C_{42}H_{43}ClO_8NH_4^+$], 760.27, found 760.8.

[0127] Step 3: **(2R,3R,4S,5S,6S)-4,5-bis(benzyloxy)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-(methoxymethyl)tetrahydro-2H-pyran-3-ol (8c)** A solution of **8b** (0.13 g, 0.17 mmol) in a mixture of DMF ((2 mL) and MeOH (0.26 mL) was added NaOMe (28 mg, 0.51 mmol), which was heated for 3 h at 85°C. Cooled to r.t. and quenched the reaction by adding H_2O to the above reaction, the organic layer was extracted with EtOAc, then washed by aq.1N HCl, dried and concentrated, the crude product was purified by flash column chromatography (silica gel, EtOAc: PE = 1:10 ~ 1: 4 ~ 1:1) to give 47 mg of **8c** as a colorless oil. Yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.30 (m, 6H), 7.27-7.21 (m, 5H), 7.08-7.04 (m, 2H), 6.95-6.93 (m, 2H), 6.79-6.76 (m, 2H), 4.96 (d, J = 11.6 Hz, 1H), 4.84 (d, J = 11.2 Hz, 1H), 4.40 (d, J = 10.4 Hz, 1H), 4.20 (d, J = 9.6 Hz, 1H), 4.11-4.07 (m, 1H), 4.02-3.95 (m, 3H), 3.86 (d, J = 10.8 Hz, 1H), 3.73-3.66 (m, 3H), 3.64-3.59 (m, 1H), 3.55-3.51 (m, 1H), 3.45 (t, J = 9.2 Hz, 1H), 3.39 (s, 3H), 2.71 (br, 1H), 1.41 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.32, 138.89, 138.57, 137.79, 137.48, 133.84, 131.14, 130.41, 129.75, 129.44, 128.53, 128.19, 127.95, 127.82, 127.63, 126.58, 114.39, 85.98, 83.56, 81.11, 78.19, 75.26, 74.73, 72.91, 71.93, 63.28, 59.60, 38.23, 14.83; LC-MS (ESI) *m/z*: calcd for [$C_{36}H_{39}ClO_6NH_4^+$], 620.28, found 620.8.

[0128] Step 4: **(2R,4R,5S,6S)-4,5-bis(benzyloxy)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-(methoxymethyl)dihydro-2H-pyran-3(4H)-one (8d)** Treatment of **8c** (47 mg, 0.78 mmol) as described above for the oxidation **6c** to **6d**, gave 13 mg of **8d** as colorless oil, yield: 28%. LC-MS (ESI) *m/z*: calcd for [$C_{36}H_{37}ClO_6NH_4^+$], 618.26, found 618.7.

[0129] Step 5: **(2R,4R,5R,6S)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-4,5-dihydroxy-2-(methoxymethyl)dihydro-2H-pyran-3(4H)-one (8)** 10% Pd/C (3 mg) was added to a solution of **8d** (13 mg, 0.022 mmol) in EtOAc (5 mL). After the resulting suspension was stirred under an atmosphere of H_2 at room temperature for 2 h. the system was bubbled with N_2, and the Pd/C was filtered off. The solution was concentrated under vacuo and purified by flash column chromatography to 3 mg of **8** as colorless oil, yield: 33%. ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.03, 167.70, 157.46, 139.309, 135.61, 134.58, 132.30, 131.00, 130.89, 130.04, 129.87, 129.80, 129.76, 129.68, 128.82, 126.30, 114.49, 80.65, 79.75, 79.26, 69.77, 65.56, 63.38, 59.68, 38.36, 14.87; LC-MS (ESI) *m/z*: calcd for [$C_{22}H_{25}ClO_6NH_4^+$], 438.17, found 438.6.

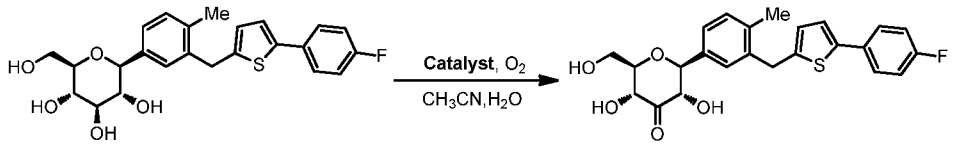
[0130] Synthesis of ((2R,3S,4R,5R,6S)-6-(4-Chloro-3-(4-ethoxybenzyl)phenyl)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)methyl acetate (9)



dapagliflozin, 24 9

[0131] To a solution of **dapagliflozin, 24** (204.4 mg, 0.5 mmol) in anhydrous pyridine (3 mL) was added AcCl (43 uL, 0.6 mmol) dropwise at -40~-30 °C under nitrogen atmosphere. The reaction mixture was stirred for 4 h at that temperature. After evaporation the organic solvents, the residue was purified by chromatography (200~300 mesh silica gel, eluted with MeOH/DCM = 1:50-1:30) to produce **9** as a white solid (74 mg, 33%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.33 (m, 1H), 7.18-7.15 (m, 2H), 7.06 (d, J = 7.6 Hz, 2H), 6.79 (d, J = 7.6 Hz, 2H), 4.32-4.27 (m, 2H), 4.04-4.02 (m, 2H), 3.98-3.94 (m, 2H), 3.61-3.55 (m, 2H), 3.46-3.35 (m, 3H), 2.03 (s, 3H), 1.36 (t, J = 6.4 Hz, 3H); LC-MS (ESI) *m/z*: calcd for [$C_{23}H_{27}ClO_7H^+$], 451.15, found 451.12.

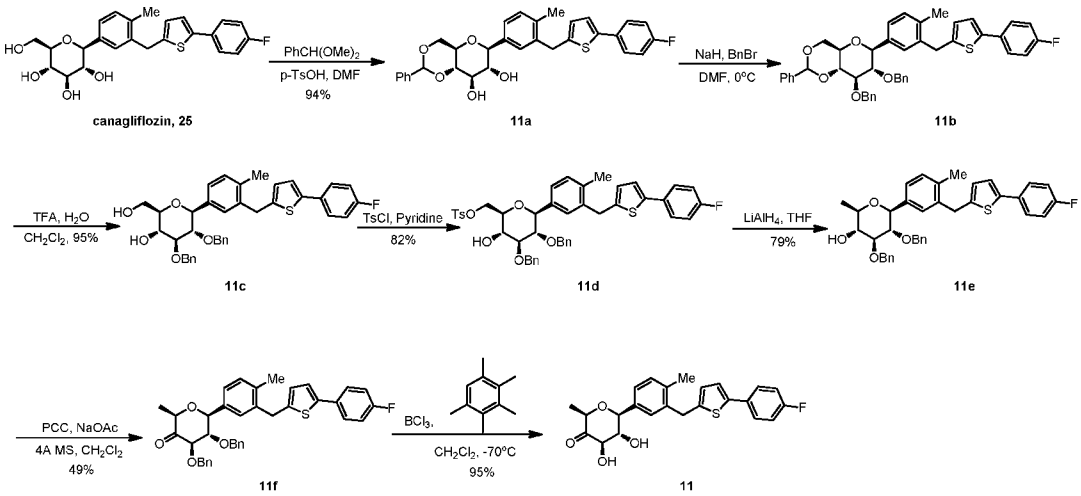
[0132] Synthesis of (2S,3S,5R,6R)-2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-3,5-dihydroxy-6-(hydroxymethyl)dihydro-2H-pyran-4(3H)-one (10)



canagliflozin, 25 10

[0133] Treatment of **canagliflozin, 25** (0.5 g, 1.12 mmol) as described above for the oxidation of dapagliflozin to **5**, gave 0.2 g of **10** as white syrup, yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.43 (m, 2H), 7.27-7.20 (m, 3H), 7.02-6.98 (m, 3H), 6.64 (d, J = 3.2 Hz, 1H), 4.45 (d, J = 9.6 Hz, 1H), 4.30 (d, J = 9.6 Hz, 1H), 4.19 (d, J = 9.6 Hz, 1H), 4.13-4.11 (m, 2H), 3.99 (d, J = 12.0 Hz, 1H), 3.89-3.85 (m, 1H), 3.47 (d, J = 9.2 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.64, 163.22, 160.77, 142.82, 141.50, 138.33, 137.34, 135.28, 130.74, 128.42, 127.05, 126.97, 126.02, 125.49, 122.63, 115.76, 115.54, 84.69, 82.98, 77.08, 72.70, 62.36, 34.02, 19.22; LC-MS (ESI) *m/z*: calcd for [$C_{24}H_{23}FO_5SNH_4^+$], 460.16, found 460.15.

[0134] Synthesis of (2R,4R,5R,6S)-6-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-4,5-dihydroxy-2-methyldihydro-2H-pyran-3(4H)-one (11)



[0135] Step 1: **(4aR,6S,7R,8R,8aS)-6-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diol (11a)** Treatment of **Canagliflozin, 25** (4.5 g, 0.01 mol) as described above for the protection of **dapagliflozin** to **4a**, gave 5.0 g of **11a** as yellow solid, yield: 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.46-7.43 (m, 2H), 7.38-7.34 (m, 3H), 7.25 (s, 1H), 7.23-7.16 (m, 2H), 7.02-6.97 (m, 3H), 6.65 (d, J = 3.6 Hz, 1H), 5.55 (s, 1H), 4.34 (dd, J = 4.8, 10.4 Hz, 1H), 4.25 (d, J = 9.6 Hz, 1H), 4.11 (s, 2H), 3.86 (t, J = 8.4 Hz, 1H), 3.74 (t, J = 10.0 Hz, 1H), 3.65-3.55 (m, 3H), 3.22 (br, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.63, 160.81, 143.10, 141.47, 138.29, 137.20, 136.91, 135.91, 130.73, 129.16, 128.88, 128.27, 127.11, 127.03, 126.34, 125.98, 125.94, 122.66, 115.79, 115.58, 101.82, 82.40, 81.14, 75.66, 74.89, 70.82, 68.92, 36.48, 19.26; LC-MS (ESI) *m/z*: calcd for [$C_{31}H_{29}FO_5SH^+$], 533.18, found 533.01.

[0136] Step 2: **(4aR,6S,7S,8R,8aR)-7,8-bis(benzyloxy)-6-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine (11b)** Treatment of **11a** (1.8 g, 3.38 mmol) as described above for the conversion of **4a** to **4b**, gave 2.29 g of **11b** as white solid, yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.6 Hz, 2H), 7.41-7.28 (m, 10H), 7.25-7.17 (m, 4H), 7.00-6.96 (m, 4H), 6.66-6.65 (m, 1H), 5.65 (s, 1H), 5.02 (d, J = 11.2 Hz, 1H), 4.85 (d, J = 11.2 Hz, 1H), 4.51 (d, J = 10.4 Hz, 1H), 4.42-4.36 (m, 2H), 4.20 (d, J = 16.0 Hz, 1H), 4.13 (d, J = 16.0 Hz, 1H), 4.01-3.92 (m, 2H), 3.88-3.79 (m, 2H), 3.68-3.59 (m, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.25,160.80, 143.34, 141.48, 138.59, 138.32, 137.83, 137.44, 136.90, 136.60, 130.70, 129.04, 128.92, 128.36, 128.26, 128.18, 128.14, 128.06, 127.66, 127.62, 127.09, 127.01, 126.46, 126.01, 125.87, 122.63, 115.78, 115.56, 101.11, 83.62, 82.79, 82.42, 75.42, 75.21, 70.80, 69.03, 34.20, 19.33.

[0137] Step 3: **(2R,3R,4S,5S,6S)-4,5-bis(benzyloxy)-6-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol (11c)** Treatment

of **11b** (1.36 g, 1.91 mmol) as described above for the deprotection of **6d** to **6**, gave 1.13 g of **11c** as yellow oil, yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 10H), 7.22-7.16 (m, 4H), 6.98-6.93 (m, 5H), 6.64 (d, J = 3.6 Hz, 1H), 4.97 (d, J = 11.6 Hz, 1H), 4.72 (d, J = 11.6 Hz, 1H), 4.32 (d, J = 10.4 Hz, 1H), 4.27 (d, J = 8.8 Hz, 1H), 4.18-4.07 (m, 4H), 3.90-3.87 (m, 2H), 3.78 (dd, J = 5.6, 12.0 Hz, 1H), 3.66 (t, J = 8.8 Hz, 1H), 3.59-3.52 (m, 2H), 3.48-3.44 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.24, 160.79, 143.28, 141.48, 138.51, 138.37, 137.63, 136.89, 136.76, 130.68, 129.00, 128.67, 128.24, 128.13, 127.97, 127.84, 127.70, 127.06, 126.98, 126.42, 125.85, 122.60, 115.75, 115.53, 85.90, 84.13, 81.68, 79.16, 75.29, 74.81, 71.03, 62.97, 34.17, 19.31; LC-MS (ESI) *m/z*: calcd for [$C_{38}H_{37}FO_5SNH_4^+$], 642.27, found 642.11.

[0138] Step 4: **((2R,3R,4S,5S,6S)-4,5-bis(benzyloxy)-6-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-3-hydroxytetrahydro-2H-pyran-2-yl)methyl 4-methylbenzenesulfonate (11d)** Treatment of **11c** (1.13 g, 1.81 mmol) as described above for the tosylation of **8a** to **8b**, gave 1.15 g of **11d** as white syrup, yield: 82%. LC-MS (ESI) *m/z*: calcd for [$C_{45}H_{43}FO_7S_2NH_4^+$], 796.28, found 796.12.

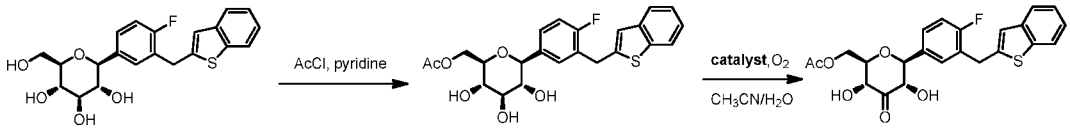
[0139] Step 5: **(2R,3R,4S,5S,6S)-4,5-bis(benzyloxy)-6-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-2-methyltetrahydro-2H-pyran-3-ol (11e)** Treatment of **11d** (1.15 g, 1.48 mmol) as described above for the conversion of **6a** to **6b**, gave 0.77 g of **11e** as white solid, yield: 79%. LC-MS (ESI) *m/z*: calcd for [$C_{38}H_{37}FO_4SH^+$], 609.25, found 608.87; [M+NH_4^+], 626.27, found 626.20.

[0140] Step 6: **(2R,4R,5S,6S)-4,5-bis(benzyloxy)-6-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-2-methyldihydro-2H-pyran-3(4H)-one (11f)** Treatment of **11e** (0.77 g, 1.26 mmol) as described above for the oxidation of **6c** to **6d**, gave 0.38 g of **11f** as yellow oil, yield: 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 1.6, 7.6 Hz, 2H), 7.41-7.30 (m, 7H), 7.25-7.21 (m, 4H), 7.02-6.97 (m, 5H), 6.68 (d, J = 3.2 Hz, 1H), 5.07 (d, J = 11.6 Hz, 1H), 4.70 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 9.6 Hz, 1H), 4.53 (d, J = 10.4 Hz, 1H), 4.32 (d, J = 9.2 Hz, 1H), 4.17 (d, J = 7.6 Hz, 2H), 4.09-4.05 (m, 2H), 3.88 (t, J = 9.6 Hz, 1H), 2.38 (s, 3H), 1.41 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.80, 163.26, 160.81, 143.32, 141.50, 138.40, 137.71, 137.67, 136.90, 136.20, 130.75, 128.86, 128.46, 128.19, 128.14, 127.92, 127.66, 127.11, 127.03, 126.27, 125.95, 122.67, 115.80, 115.58, 86.32, 85.94, 81.65, 77.38, 75.12, 73.94, 34.19, 19.36, 14.12; LC-MS (ESI) *m/z*: calcd for [$C_{38}H_{35}FO_4SNH_4^+$], 624.26, found 623.99.

[0141] Step 7: **(2R,4R,5R,6S)-6-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-4,5-dihydroxy-2-methyldihydro-2H-pyran-3(4H)-one (11)** To a cold solution of **11f** (80 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was added pentamethylbenzene (0.15 g, 0.98

mmol) and BCl_3 (1.0 M in hexane; 0.52 mL, 0.52 mmol) and the mixture was stirred at -78°C for 4 h. The reaction mixture was quenched by adding MeOH at -78°C then warmed up to rt. The solution was evaporated *in vacuo* and the resulting residue was purified by flash column chromatography (EA: PE = 1: 2 ~ EA: MeOH = 30: 1) to give 52 mg of **11** as yellow oil, yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.27-7.19 (m, 3H), 7.03-6.99 (m, 3H), 6.66 (d, J = 3.6 Hz, 1H), 4.52 (d, J = 9.6 Hz, 1H), 4.29 (d, J = 9.2 Hz, 1H), 4.15-4.11 (m, 3H), 3.76 (t, J = 9.6 Hz, 1H), 2.32 (s, 3H), 1.37 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.86, 163.29, 160.84, 157.05, 142.99, 141.55, 138.45, 137.14, 135.09, 130.84, 128.74, 127.13, 127.05, 126.04, 125.80, 122.28, 115.81, 115.60, 81.26, 79.83, 79.24, 76.70, 34.11, 19.29, 14.02; LC-MS (ESI) *m/z*: calcd for [$C_{24}H_{23}FO_4SNa^+$], 449.12, found 449.12.

[0142] Syntheses of ((2R,3R,5S,6S)-6-(3-(benzo[b]thiophen-2-ylmethyl)-4-fluorophenyl)-3,5-dihydroxy-4-oxotetrahydro-2H-pyran-2-yl)methyl acetate (12) and ((2R,3S,4R,5R,6S)-6-(3-(benzo[b]thiophen-2-ylmethyl)-4-fluorophenyl)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)methyl acetate (15)



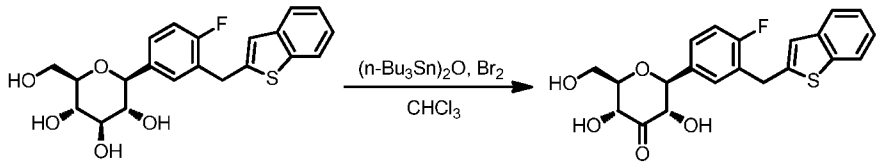
ipragliflozin, 26 15 12

[0143] Step 1: ((2R,3S,4R,5R,6S)-6-(3-(benzo[b]thiophen-2-ylmethyl)-4-fluorophenyl)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)methyl acetate (15) Treatment of as described above for the conversion of **dapagliflozin** to **9**, **ipragliflozin, 26** (510 mg, 1.26 mmol) gave 230 mg of **15** as a white solid, yield: 41%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.32-7.26 (m, 4H), 7.19-7.15 (m, 2H), 5.24 (d, J = 5.6 Hz, 1H), 5.08 (d, J = 4.8 Hz, 1H), 4.91 (d, J = 5.6 Hz, 1H), 4.39 (d, J = 11.2 Hz, 1H), 4.27 (s, 2H), 4.09 (d, J = 9.2 Hz, 1H), 4.02 (dd, J = 6.8, 11.6 Hz, 1H), 3.50-3.47 (m, 1H), 3.31 (dd, J = 4.8, 8.4 Hz, 1H), 3.23-3.15 (m, 2H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.36, 160.83 (d, $J_{C,F}$ = 242.8 Hz), 143.67, 139.62, 138.94, 136.51 (d, J = 3.4 Hz), 130.41 (d, J = 3.9 Hz), 128.13 (d, J = 7.6 Hz), 125.67 (d, J = 13.0 Hz), 124.32, 123.84, 123.06, 122.24, 121.73, 114.87 (d, J = 21.8 Hz), 80.57, 77.98, 77.79, 74.64, 70.30, 64.24, 29.45 (d, J = 2.9 Hz), 20.67. LC-MS (ESI) *m/z*: calcd for [$C_{23}H_{23}FO_6SH^+$] 447.13, found 447.2.

[0144] Step 2: ((2R,3R,5S,6S)-6-(3-(benzo[b]thiophen-2-ylmethyl)-4-fluorophenyl)-3,5-dihydroxy-4-oxotetrahydro-2H-pyran-2-yl)methyl acetate (12) Treatment of **15** (80 mg, 0.18 mmol) as described above for the oxidation of **dapagliflozin** to **5**, gave 10 mg of **12**, yield: 13%. ^{1}H NMR (400 MHz, MeOD) δ 7.74 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.46 (dd,

J = 2.0, 7.6 Hz, 1H), 7.40-7.36 (m, 1H), 7.29-7.21 (m, 2H), 7.15-7.10 (m, 1H), 7.06 (s, 1H), 4.51 (dd, *J* = 2.0, 12.0 Hz, 1H), 4.37-4.27 (m, 4H), 4.25 (s, 2H), 3.71-3.67 (m, 1H), 2.01 (s, 3H); LC-MS (ESI) *m/z*: calcd for $[C_{23}H_{21}FO_6SH^+]$ 445.11, found 445.2.

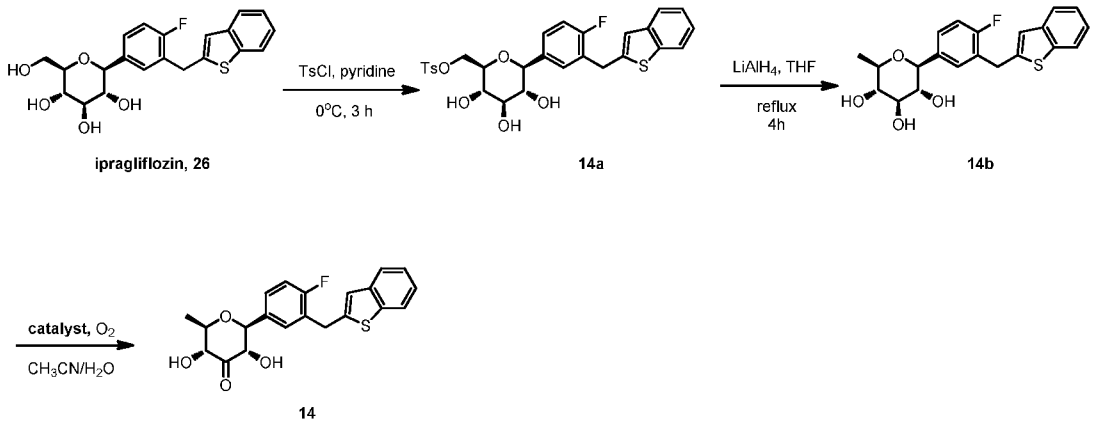
[0145] Synthesis of (2S,3S,5R,6R)-2-(3-(benzo[b]thiophen-2-ylmethyl)-4-fluorophenyl)-3,5-dihydroxy-6-(hydroxymethyl)dihydro-2H-pyran-4(3H)-one (13)



ipragliflozin, 26 13

[0146] To a mixture of **ipragliflozin**, **26** (0.35 g, 0.87 mmol) and an excess of 3A molecular sieves in anhydrous $CHCl_3$ (20 mL) under N_2 was added $(n\text{-}Bu_3Sn)_2O$ (0.88 mL, 1.74 mmol). The mixture was heated under refluxed for 2 h and then cooled to r.t., 1M Br_2 in CH_2Cl_2 (2.7 mL) was added dropwise at 0°C with stirring until the solution was faintly colored (40 min). The mixture was extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash column chromatography (silica gel, EA: MeOH = 20: 1) to give 60 mg of **13**, yield: 17%. ^{1}H NMR (400 MHz, MeOD) δ 7.75-7.70 (m, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 2.0, 7.2 Hz, 1H), 7.47-7.42 (m, 1H), 7.28-7.21 (m, 2H), 7.14-7.10 (m, 1H), 7.03 (s, 1H), 4.40 (d, *J* = 10.0 Hz, 1H), 4.26-4.23 (m, 4H), 3.95 (dd, *J* = 2.0, 12.0 Hz, 1H), 3.84-3.79 (m, 1H), 3.51-3.47 (m, 1H); ^{13}C NMR (100 MHz, MeOD) δ 208.38, 163.22 (d, $J_{C,F}$ = 244.1 Hz), 141.43 (d, *J* = 36.3 Hz), 136.50 (d, *J* = 3.4 Hz), 131.60 (d, *J* = 4.4 Hz), 129.20 (d, *J* = 8.5 Hz), 127.75 (d, *J* = 16.1 Hz), 126.33 (d, *J* = 14.2 Hz), 125.21, 124.79, 123.99, 123.64 (d, *J* = 17.2 Hz), 122.97, 122.86, 116.22 (d, *J* = 22.2 Hz), 85.16, 84.60, 78.68, 74.02, 62.88, 30.71 (d, *J* = 3.1 Hz); LC-MS (ESI) *m/z*: calcd for $[C_{21}H_{19}FO_5SNH_4^+]$, 420.13, found 420.1.

[0147] Synthesis of (2S,3S,5R,6R)-2-(3-(benzo[b]thiophen-2-ylmethyl)-4-fluorophenyl)-3,5-dihydroxy-6-methyldihydro-2H-pyran-4(3H)-one (14)



ipragliflozin, 26 14a 14b

14

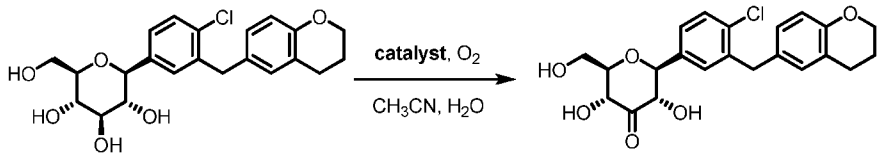
[0148] Step 1: ((2R,3S,4R,5R,6S)-6-(3-(benzo[b]thiophen-2-ylmethyl)-4-fluorophenyl)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)methyl 4-methylbenzenesulfonate (14a) Treatment of **ipragliflozin**, **26** (1.5 g, 3.71 mmol) as described above for the protection of **dapagliflozin** to **6a**, gave 1.8 g of **14a**, yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (t, J = 2.0 Hz, 1H), 7.75 (t, J = 2.0 Hz, 1H), 7.73-7.71 (m, 1H), 7.66 (dd, J = 1.2, 7.2 Hz, 1H), 7.31-7.26 (m, 6H), 7.24-7.22 (m, 2H), 7.07 (t, J = 9.2 Hz, 1H), 7.04 (s, 1H), 4.39 (dd, J = 4.0, 11.2 Hz, 1H), 4.25-4.22 (m, 3H), 4.10 (d, J = 9.6 Hz, 1H), 3.71 (t, J = 9.2 Hz, 1H), 3.63 (t, J = 8.8 Hz, 1H), 3.57-3.53 (m, 1H), 3.41 (t, J = 9.2 Hz, 1H), 2.39 (s, 3H); LC-MS (ESI) *m/z*: calcd for [$C_{28}H_{27}FO_7S_2H^+$], 559.13, found 559.1.

[0149] Step 2: (2S,3R,4S,5S,6R)-2-(3-(benzo[b]thiophen-2-ylmethyl)-4-fluorophenyl)-6-methyltetrahydro-2H-pyran-3,4,5-triol (14b) Treatment of **14a** (1.3 g, 2.33 mmol) as described above for the conversion of **6a** to **6b**, gave 0.6 g of **14b**, yield: 66%. ^{1}H NMR (400 MHz, MeOD) δ 7.74-7.72 (m, 1H), 7.67 (dd, J = 1.2, 7.2 Hz, 1H), 7.39 (dd, J = 2.0, 7.2 Hz, 1H), 7.33-7.28 (m, 1H), 7.26 (dd, J = 1.6, 4.8 Hz, 1H), 7.23 (dd, J = 1.6, 7.2 Hz, 1H), 7.11-7.08 (m, 1H), 7.06 (s, 1H), 4.31-4.22 (m, 2H), 4.10 (d, J = 9.2 Hz, 1H), 3.43-3.38 (m, 2H), 3.11 (t, J = 9.2 Hz, 1H), 1.29 (d, J = 6.0 Hz, 3H); LC-MS (ESI) *m/z*: calcd for [$C_{21}H_{21}FO_4SH^+$], 389.12, found 389.3.

[0150] Step 3: (2S,3S,5R,6R)-2-(3-(benzo[b]thiophen-2-ylmethyl)-4-fluorophenyl)-3,5-dihydroxy-6-methyldihydro-2H-pyran-4(3H)-one (14) Treatment of **14b** (0.15 g, 0.39 mmol) as described above for the oxidation of **dapagliflozin** to **5**, gave 40 mg of **14**, yield: 27%. ^{1}H NMR (400 MHz, MeOD) δ 7.75-7.72 (m, 1H), 7.67-7.65 (m, 1H), 7.46 (dd, J = 2.0, 7.2 Hz, 1H), 7.41-7.37 (m, 1H), 7.28 (dt, J = 1.2, 7.2 Hz, 1H), 7.23 (dt, J = 1.2, 7.2 Hz, 1H), 7.15 (dd, J = 8.8, 10.0 Hz, 1H), 7.06 (s, 1H), 4.28 (m, 2H), 4.26-4.20 (m, 2H), 4.06 (dd, J = 1.2, 9.6 Hz, 1H), 3.56-3.50 (m, 1H), 1.45 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, MeOD) δ 207.85, 163.19 (d, $J_{C,F}$ = 244.0 Hz), 144.79, 141.45 (d, J = 35.3 Hz), 136.68 (d, J = 3.5 Hz), 131.42 (d, J = 4.4 Hz),

129.02 (d, J = 8.4 Hz), 127.79 (d, J = 16.1 Hz), 125.21, 124.80, 124.01, 122.98, 122.92, 116.24 (d, J = 22.4 Hz), 85.00, 80.41, 79.32, 78.76, 30.68 (d, J = 3.4 Hz), 19.37; LC-MS (ESI) *m/z*: calcd for $[C_{21}H_{19}FO_4SH^+]$ 387.11, found 387.2.

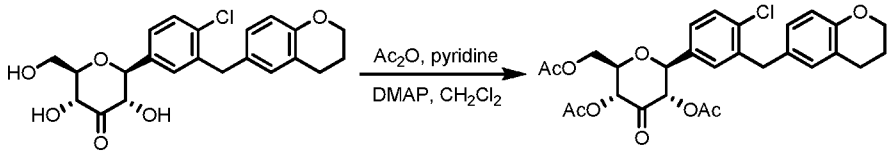
[0151] Synthesis of (2S,3S,5R,6R)-2-(4-chloro-3-(chroman-6-ylmethyl)phenyl)-3,5-dihydroxy-6-(hydroxymethyl)dihydro-2H-pyran-4(3H)-one (16)



16a 16

[0152] **16a** was prepared using a method publicated in **US 2011/0171159**, treatment of **16a** (0.45 g, 1.07 mmol) as described above for the oxidation of **dapagliflozin** to **5**, gave 0.22 g of **16** as a light yellow solid, yield: 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 2.4, 8.0 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 2.0, 8.0 Hz, 1H), 6.86 (m, 1H), 6.72 (d, J = 8.0 Hz, 1H), 4.49 (dd, J = 1.6, 9.6 Hz, 1H), 4.28 (dd, J = 1.6, 9.2 Hz, 1H), 4.20 (d, J = 9.6 Hz, 1H), 4.16 (t, J = 5.2 Hz, 2H), 4.08-3.96 (m, 3H), 3.93 (dd, J = 4.8, 12.4 Hz, 1H), 3.52-3.48 (m, 1H), 2.74 (t, J = 6.4 Hz, 2H), 2.01-1.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.37, 153.39, 139.40, 136.05, 134.78, 130.52, 130.11, 129.78, 129.76, 127.68, 125.84, 122.16, 116.66, 84.31, 83.20, 77.05, 72.72, 66.41, 62.56, 38.36, 24.88, 22.34; LC-MS (ESI) *m/z*: calcd for $[C_{22}H_{23}ClO_6NH_4^+]$, 436.15, found 436.38.

[0153] Synthesis of (2R,3R,5S,6S)-2-(acetoxymethyl)-6-(4-chloro-3-(chroman-6-ylmethyl)phenyl)-4-oxotetrahydro-2H-pyran-3,5-diyl diacetate (17)

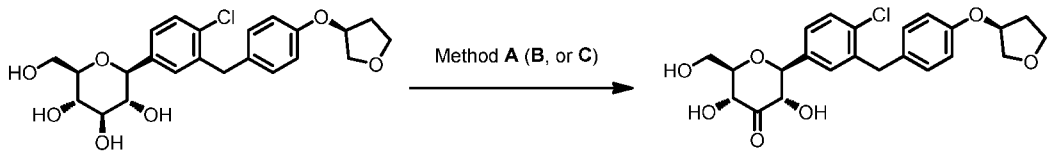


16 17

[0154] Compound **16** (0.1 g, 0.239 mmol) was dissolved in CH_2Cl_2 (10.0 mL), Then Ac_2O (0.24 g, 2.39 mmol), pyridine (0.19 g, 2.39 mmol), and catalytic DMAP (1.5 mg 0.012 mmol) was added. The mixture was stirred at room temperature overnight. LC-MS indicated completion of the reaction, Water (10 mL) was added to the reaction mixture and the organic layer was separated from the aqueous layer. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried over $NaSO_4$, and concentrated to produce a residue, which was purified by chromatography (silica gel, EtOAc: PE = 5: 1 ~ 10: 1) to produce 60 mg of **17** as a white solid, yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 1H), 7.26-7.20 (m, 1H), 7.12-7.11 (m, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.83(s, 1H), 6.72 (d, J = 8.0

Hz, 1H), 5.44 (d, J = 10.4 Hz, 1H), 5.29 (d, J = 10.0 Hz, 1H), 4.54 (d, J = 10.0 Hz, 1H), 4.35-4.30 (m, 2H), 4.17-4.14 (m, 2H), 4.14-3.94 (m, 3H), 2.75 (t, J = 6.4 Hz, 2H), 2.19 (s, 3H), 2.10 (s, 3H), 2.02-1.97 (m, 2H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.73, 170.54, 168.88, 168.55, 153.46, 139.43, 135.00, 134.82, 130.43, 130.10, 129.90, 129.44, 127.67, 125.53, 122.22, 116.72, 80.91, 77.57, 77.17, 72.93, 66.40, 62.54, 38.26, 24.86, 22.31, 20.73, 20.30, 20.06; LC-MS (ESI) *m/z*: calcd for $[C_{28}H_{29}ClO_9NH_4^+]$, 562.18, found 562.47.

[0155] Synthesis of (2S,3S,5R,6R)-2-(4-Chloro-3-(4-((R)-tetrahydrofuran-3-yloxy)benzyl)phenyl)-3,5-dihydroxy-6-(hydroxymethyl)dihydro-2H-pyran-4(3H)-one (18)



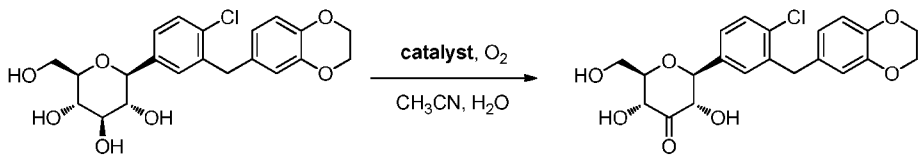
empagliflozin, 27 18

Method **A**: $(Bu_3Sn)_2O$, Br_2, $CHCl_3$
Method **B**: ***Catalyst***, 2,6-dichloro-1,4-benzoquinone, CH_3CN, H_2O
Method **C**: ***Catalyst***, O_2, CH_3CN, H_2O

[0156] Method **A:** Treatment of **empagliflozin, 27** (0.5 g, 1.11 mmol) as described above for the oxidation of **ipragliflozin** to **13**, gave 0.13 g of **18** as a white solid, yield: 26%.

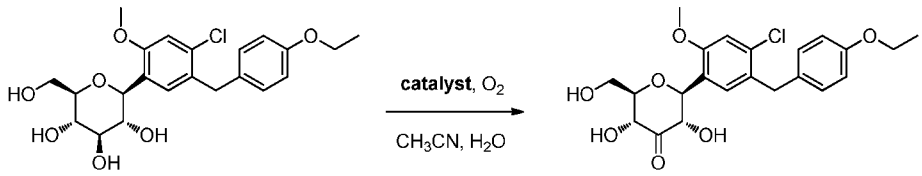
[0157] Method **B**: **Empagliflozin, 27** (50 mg,0.11 mmol) and 2,6-dichloro-1,4-benzoquinone (59 mg, 0.33 mmol) were suspended in CH_3CN/H_2O (2.0 mL, 10:1). Then **Catalyst A (B, or C)** (5.8 mg, 5 mol %) was added, and the mixture was stirred at room temperature for 1.5 h. LC-MS showed the reaction to be completed. After purification, gave 20 mg of **18**, yield: 45%.

[0158] Method **C**: Treatment of **empagliflozin, 27** (50 mg, 0.11 mmol) as described above for the oxidation of **dapagliflozin** to **5**, gave 23 mg of **18**, yield: 47% . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.41 (m, 1H), 7.23-7.12 (m, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 4.97-4.94 (m, 1H), 4.27 (d, J = 9.2 Hz, 1H), 4.21 (d, J = 9.2 Hz, 1H), 4.01-3.99 (m, 2H), 3.88-3.70 (m, 6H), 3.63-3.41 (m, 2H), 2.22-2.13 (m, 1H), 1.96-1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.57, 155.78, 139.02, 136.54, 134.54, 131.58, 130.02, 129.95, 129.75, 126.20, 115.37, 83.92, 82.87, 77.19, 77.11, 72.97, 72.67, 67.16, 62.16, 38.31, 32.87; LC-MS (ESI) *m/z*: calcd for $[C_{23}H_{25}ClO_7H^+]$, 449.14, found 449.12.



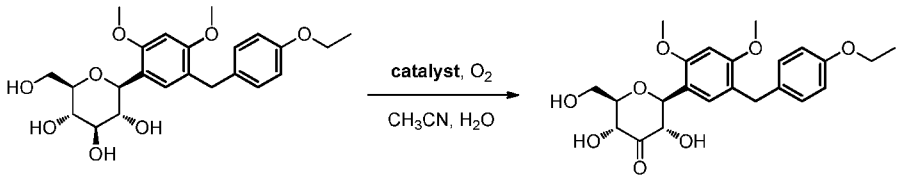
20a 20

(2S,3S,5R,6R)-2-(4-Chloro-3-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)phenyl)-3,5-dihydroxy-6-(hydroxymethyl)dihydro-2H-pyran-4(3H)-one (20) **20a** was prepared using a method publicated in **US 2011/0171159**, treatment of **20a** (150 mg, 0.35 mmol) as described above for the oxidation of **dapagliflozin** to **5**, gave 70 mg of **20** as a white solid, yield: 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 1H), 7.28-7.26 (m, 1H), 7.24-7.22 (m, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.69-6.66 (m, 2H), 4.49 (dd, J = 2.0, 10.0 Hz, 1H), 4.28 (dd, J = 2.0, 10.0 Hz, 1H), 4.23 (s, 4H), 4.20 (d, J = 9.6 Hz, 1H), 4.06 (d, J = 9.6 Hz, 1H), 4.04 (d, J = 15.6 Hz, 1H), 3.98 (d, J = 15.6 Hz, 1H), 3.94-3.89 (m, 1H), 3.53-3.49 (m, 1H) ; LC-MS (ESI) *m/z*: calcd for $[C_{21}H_{21}ClO_7NH_4^+]$, 438.13, found 438.18.



21a 21

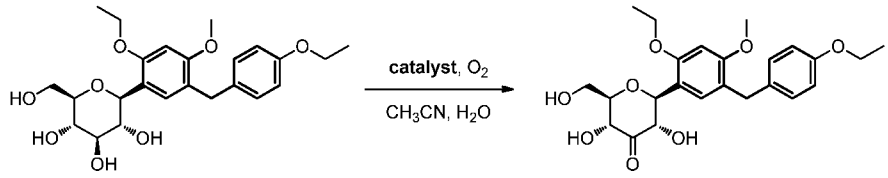
(2S,3S,5R,6R)-2-(4-chloro-5-(4-ethoxybenzyl)-2-methoxyphenyl)-3,5-dihydroxy-6-(hydroxymethyl)dihydro-2H-pyran-4(3H)-one (21) **21a** was prepared using a method publicated in **EP1845095**, treatment of **21a** (150 mg, 0.34 mmol) as described above for the oxidation of **dapagliflozin** to **5**, gave 63 mg of **21** as a white solid, yield: 42%. ^{1}H NMR (400 MHz, CDCl3) δ 7.20 (s, 1H), 7.09-7.07 (m, 2H), 6.96 (s, 1H), 6.83-6.81 (m, 2H), 4.67 (d, J = 9.6 Hz, 1H), 4.48 (dd, J = 1.6, 9.6 Hz, 1H), 4.44 (dd, J = 1.6, 9.6 Hz, 1H), 4.03-3.98 (m, 5H), 3.86 (dd, J = 4.8, 12.0 Hz, 1H), 3.82 (s, 3H), 3.52-3.48 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H); LC-MS (ESI) *m/z*: calcd for $[C_{22}H_{25}ClO_7NH_4^+]$, 455.16, found 455.70.



22a 22

(2S,3S,5R,6R)-2-(5-(4-ethoxybenzyl)-2,4-dimethoxyphenyl)-3,5-dihydroxy-6-(hydroxymethyl)dihydro-2H-pyran-4(3H)-one (22) **22a** was prepared using a method publicated in **EP1845095**, treatment of **22a** (150 mg, 0.35 mmol) as described above for the oxidation of **dapagliflozin** to **5**, gave 70 mg of **22** as a white solid, yield: 47%. ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.10-7.07 (m, 3H), 6.81-6.77(m, 2H), 6.48 (s, 1H), 4.66 (d, J = 9.6 Hz, 1H), 4.53 (dd, J = 2.0, 9.6 Hz, 1H), 4.43 (dd, J = 2.0, 9.6 Hz, 1H), 4.00 (q, J = 6.8 Hz, 2H), 3.99 (d, J =

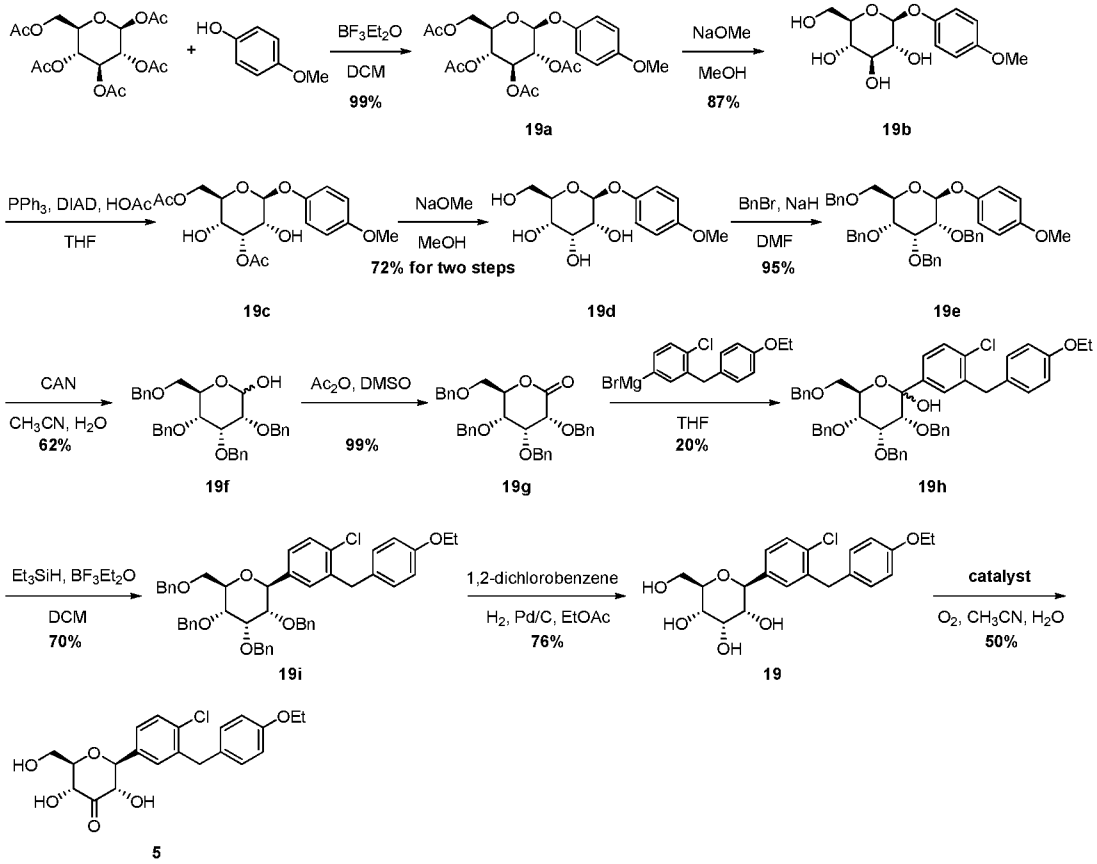
9.6 Hz, 1H), 3.87-3.84 (m, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.50-3.46 (m, 1H), 1.39 (t, J = 6.8 Hz, 3H) ; LC-MS (ESI) *m/z*: calcd for [$C_{21}H_{21}ClO_7NH_4^+$], 450.21, found 450.11.



23a 23

(2S,3S,5R,6R)-2-(2-ethoxy-5-(4-ethoxybenzyl)-4-methoxyphenyl)-3,5-dihydroxy-6-(hydroxymethyl)dihydro-2H-pyran-4(3H)-one (23) **23a** was prepared using a similar method publicated in **EP1845095**, treatment of **23a** (203 mg, 0.45 mmol) as described above for the oxidation of **dapagliflozin** to **5**, gave 65 mg of **23** as a white solid, yield: 32%. ^{1}H NMR(400 MHz, $CDCl_3$) δ ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.08-7.06 (m, 3H), 6.78 (m, 2H), 6.46 (s, 1H), 4.62 (d, J = 9.6 Hz, 1H), 4.57 (dd, J = 2.0, 9.6 Hz, 1H), 4.41 (dd, J = 2.0, 9.6 Hz, 1H), 4.08 (q, J = 6.8 Hz, 2H), 3.97 (m, J = 7.2 Hz, 2H), 3.85-3.81 (m, 4H), 3.79 (s, 3H), 3.48-3.43 (m, 1H), 1.38 (t, J = 6.8 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H) ; LC-MS (ESI) *m/z*: calcd for [$C_{21}H_{21}ClO_7NH_4^+$], 464.23, found 464.37.

[0159] Example of 3-oxo glucopyranoside (compound 5) synthesis route 1



[0160] Step 1: (2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(4-methoxyphenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (19a) To a cold (0 °C) solution of 1,2,3,4,6-penta-*O*-acetyl-*β*-D-glucopyranose (50.0 g, 128 mmol) and 4-methoxyphenol (19.1 g, 154 mmol) in dry CH_2Cl_2 (400 mL) was added $BF_3 \cdot Et_2O$ (17.7 mL, 141 mmol) under Ar. After stirring for 16 h, the mixture was diluted with DCM (500 mL) and washed with water (200 mL), saturated aq $NaHCO_3$ (200 mL), and water (2×200 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was recrystallized from EtOAc and Petroleum ether to give **19a** as a white solid (57.5 g, 99%); LC-MS (ESI): 472.77 $[M+NH_4]^+$.

[0161] Step 2: (2R,3S,4S,5R,6S)-2-(hydroxymethyl)-6-(4-methoxyphenoxy)tetrahydro-2H-pyran-3,4,5-triol (19b) To a solution of **19a** (20.0 g, 44 mmol) in MeOH (200 mL) was added a solution of NaOMe in MeOH (1M, 17.6 mL, 17.6 mmol). The reaction mixture was stirred for 2 h, then neutralised by addition of Dowex 50wx8 (100-200, H^+). The mixture was filtered and concentrated to give a residue, which was washed with EtOAc (30 mL) to afford **19b** as a white solid (10.9 g, 87%); LC-MS (ESI): 309.36 $[M+Na]^+$.

[0162] Step 3: ((2R,3R,4R,5R,6S)-4-acetoxy-3,5-dihydroxy-6-(4-methoxyphenoxy)tetrahydro-2H-pyran-2-yl)methyl acetate (19c) To a suspension of **19b**

(20.0 g, 70 mmol) and 3 Å activated molecular sieves (5.0 g) in dry THF (500 mL), acetic acid (12.0 mL, 210 mmol) and triphenylphosphine (55.0 g, 210 mmol) were added and the resulting solution heated at 60 °C for 20 min. To this mixture, diisopropyl azodicarboxylic acid (41.3 mL, 210 mmol) was added dropwise over 20 min and the solution refluxed for 3 h, after which the solution was cooled to room temperature and filtered. The filtrate was condensed and dissolved in EtOAc/ PE (2/3, 500 mL), stirred, filtered to remove PPh_3O, the filtrate obtained was condensed again and dissolved in EtOAc/ PE (2/3, 200 mL), stirred, filtered to remove another PPh_3O. The filtrate was concentrated to give a dark red oil, which was used in the next step without further purification.

[0163] Step 4: (2R,3S,4R,5R,6S)-2-(hydroxymethyl)-6-(4-methoxyphenoxy)tetrahydro-2H-pyran-3,4,5-triol (19d) To a solution of dark red oil obtained in the last step in MeOH (200 mL) was added a solution of NaOMe in MeOH (1M, 30 mL, 30 mmol mmol). The reaction mixture was stirred for 2 h, then neutralised by addition of Dowex 50wx8 (100-200, H^+). The mixture was filtered and concentrated to give a residue, which was dissolved in DCM (300 mL), stirred, and filtered to give first batch of compound **19d** as a white solid (8.5 g). The filtrate was condensed and purified by column chromatography (200~300 mesh silica gel, eluted with MeOH/DCM = 1:30-1:10) to afford another batch of compound **19d** as a white solid (5.8 g), total yield for two steps is 72%: ^1H NMR (400 MHz, CD_3OD) δ 7.02 (d, J = 9.2 Hz, 2H), 6.81 (d, J = 9.2 Hz, 2H), 5.11 (d, J = 8.0 Hz, 1H), 4.11 (t, J = 2.8 Hz, 1H), 3.85 (dd, J = 2.0, 11.6 Hz, 1H), 3.81-3.76 (m, 1H), 3.72 (s, 3H), 3.68-3.64 (m, 1H), 3.54 (dd, J = 2.8, 11.6 Hz, 1H), 3.54 (t, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 154.22, 151.75, 117.57, 114.43, 99.56, 74.64, 71.55, 70.35, 67.19, 61.10, 55.38; LC-MS (ESI): 304.32 $[M+NH_4]^+$.

[0164] Step 5: (2R,3R,4R,5R,6S)-3,4,5-tris(benzyloxy)-2-(benzyloxymethyl)-6-(4-methoxyphenoxy)tetrahydro-2H-pyran (19e) NaH (6.3 g, 157.2 mmol) was added to a solution of compound **19d** (10.0 g, 34.9 mmol) in dry DMF (150 mL) at 0 °C. After stirring for 30 min, a solution of benzyl bromide (20.7 mL, 174.6 mmol) in dry DMF (50 mL) was added dropwise at 0 °C. The mixture was stirred at room temperature for 2 h, then poured into a saturated aqueous NaCl solution (100 mL), and extracted with ethyl acetate (3×200 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated to produce a residue, which was purified by column chromatography (200~300 mesh silica gel, eluted with EtOAc/PE = 1:10-1:5) to afford compound **19e** as a white solid (21.0 g, 95%); LC-MS (ESI): 664.61 $[M+NH_4]^+$.

[0165] Step 6: (3R,4R,5R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-ol (19f) To a cooled solution of compound **19e** (14.1 g, 21.8 mmol) in acetonitrile (420

mL), a solution of CAN (28.8 g, 52.4 mmol) in H_2O (105 mL) was added dropwise at -15 °C. The reaction mixture was stirred at -15 °C for 2 h and then partitioned between DCM (400 mL) and H_2O (50 mL). The aqueous layer was extracted with DCM (200 mL). The combined organic extracts were washed with $NaHCO_3$ saturated aqueous solution (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated to produce a residue, which was purified by column chromatography (200~300 mesh silica gel, eluted with EtOAc/PE = 1:20-1:5-1:3) to give compound **19f** as a yellow solid (7.1 g, 62%); LC-MS (ESI): 558.70 $[M+NH_4]^+$.

[0166] Step 7: (3R,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-one (19g) Acetic anhydride (26.6 mL, 280 mmol) was added to a solution of compound **19f** (9.0 g, 16.7 mmol) in anhydrous DMSO (40 mL) at 30 °C. The reaction mixture was stirred overnight at 30 °C. The reaction mixture was poured into ice-water (50 mL), extracted with DCM (3×100 mL). The combined organic phase was washed with H_2O(30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated to produce a residue, which was purified by column chromatography (200~300 mesh silica gel, eluted with EtOAc/PE = 1:20-1:6) to give compound **19g** as a white solid (8.7 g, 99%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (m, 18H), 7.24-7.16 (m, 2H), 5.11 (d, *J* = 12.4 Hz, 1H), 4.94 (d, *J* = 12.0 Hz, 1H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.64-4.60 (m, 2H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.33 (d, *J* = 12.0 Hz, 1H), 4.17 (t, *J* = 2.0 Hz, 1H), 3.91 (dd, *J* =2.0, 9.2 Hz, 1H), 3.86 (d, *J* = 2.0 Hz, 1H), 3.76 (dd, *J* = 2.0, 11.2 Hz, 1H), 3.73 (dd, *J* = 2.0, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.04, 138.11, 137.77, 137.58, 137.17, 128.51, 128.50, 128.46, 128.44, 128.26, 128.19, 128.12, 128.10, 127.96, 127.90, 127.89, 127.85, 127.84, 127.80, 127.78, 127.64, 78.58, 76.53, 73.56, 73.54, 73.49, 73.42, 73.38, 73.09, 72.92, 72.86, 72.53, 71.86, 68.04; LC-MS (ESI): 556.55 $[M+NH_4]^+$.

[0167] Step 8: (3R,4R,5R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran-2-ol (19h) To an ice-cold solution of compound **19g** (540 mg, 1.0 mmol) in anhydrous THF (10 mL) was added a solution of (4-chloro-3-(4-ethoxybenzyl)phenyl)magnesium bromide in anhydrous THF (10 mL), which was prepared freshly from 4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (486 mg, 1.5 mmol) and magnesium (54 mg, 2.25 mmol). The reaction mixture was then allowed to stir at room temperature overnight, then quenched with saturated NH_4Cl aqueous solution (10 mL) and extracted with ethyl acetate (2×40 mL). The combined organic phase was washed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated to produce a residue, which was purified by column chromatography (200~300 mesh silica gel, eluted with EtOAc/PE = 1:20-1:10) to give compound **19h** as a white solid (150 mg, 20%); LC-MS (ESI): 803.36 $[M+NH_4]^+$.

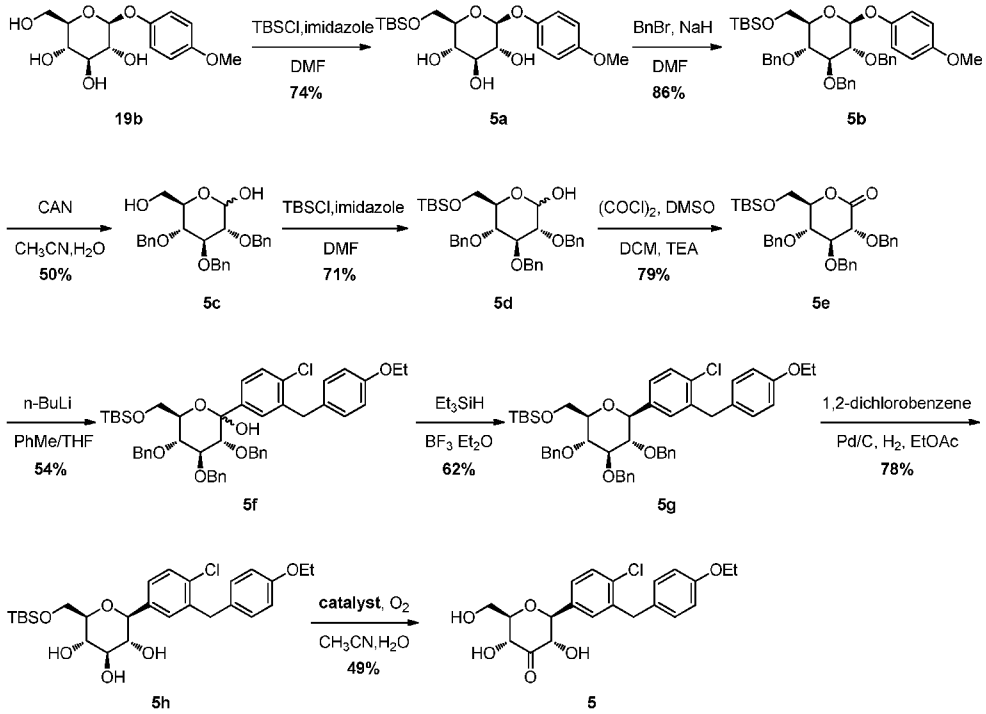
[0168] Step 9: (2R,3R,4S,5S,6S)-3,4,5-tris(benzyloxy)-2-(benzyloxymethyl)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran (19i) To a solution of compound **19h** (150 mg, 0.19 mmol) in anhydrous DCM (5 mL) was added Et_3SiH (0.06 mL, 0.38 mmol) and $BF_3 \cdot Et_2O$ (0.03 mL, 0.21 mol) dropwise at -20 °C under N_2 atmosphere. The reaction mixture was allowed to stir at -20 °C for 3 h. Saturated $NaHCO_3$ aqueous solution (5 mL) was added to the reaction mixture and the organic layer was separated from the aqueous layer. The aqueous layer was extracted with DCM (3×10 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated to produce a residue, which was purified by chromatography (200~300 mesh silica gel, eluted with EtOAc/PE = 1:20-1:10) to produce compound **19i** as a white solid (103 g, 70%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.38 (dd, *J* = 2.0, 7.2 Hz, 2H), 7.32-7.17 (m, 19H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.90 (dd, *J* = 2.0, 7.2 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.90 (d, *J* = 12.0 Hz, 1H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 9.6 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.46 (t, *J* = 2.4 Hz, 1H), 4.12 (d, *J* = 12.0 Hz, 1H), 4.09-4.06 (m, 1H), 4.01-3.98 (m, 3H), 3.94 (q, *J* = 6.8 Hz, 2H), 3.76 (dd, *J* = 4.0, 11.2 Hz, 1H), 3.73 (dd, *J* = 2.0, 11.2 Hz, 1H), 3.59 (dd, *J* = 2.4, 10.0 Hz, 1H), 3.20 (dd, *J* = 2.4, 10.0 Hz, 1H), 1.37 (t, *J* = 6.8 Hz, 3H); LC-MS (ESI) : 786.76 $[M+NH_4]^+$.

[0169] Step 10: (2S,3R,4S,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (19) To a solution of compound **19i** (103 mg, 0.13 mmol), 1,2-dichlorobenzene (96 mg, 0.65 mmol) in EtOAc (5 mL) was added Pd/C (10 wt%; 10 mg) and the mixture was stirred at room temperature for 2 h under H_2 balloon. The reaction mixture was filtered through celite and the filtrate was concentrated to give a residue, which was purified by chromatography (200~300 mesh silica gel, eluted with MeOH/DCM = 1:30-1:15) to produce compound **19** as a white solid (41 mg, 76%): ^1H NMR (400 MHz, CD_3OD) δ 7.32-7.31 (m, 2H), 7.28-7.26 (m, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 4.43 (d, *J* = 9.6 Hz, 1H), 4.07 (t, *J* = 2.8 Hz, 1H), 4.01 (d, *J* = 7.6 Hz, 2H), 3.98 (q, *J* = 6.8 Hz, 2H), 3.84 (d, *J* = 10.0 Hz, 1H), 3.73-3.65 (m, 2H), 3.57 (dd, *J* = 2.8, 9.6 Hz, 1H), 3.42 (dd, *J* = 2.8, 9.6 Hz, 1H), 1.34 (t, *J* = 6.8 Hz, 3H);^{13}C NMR (100 MHz, CD_3OD) δ 158.75, 140.57, 139.72, 134.22, 132.91, 131.95, 130.76, 130.00, 128.17, 115.38, 78.00, 77.40, 73.77, 72.96, 69.09, 64.40, 63.34, 39.23, 15.19; LC-MS (ESI) : 426.44 $[M+NH_4]^+$.

[0170] Step 11: (2S,3S,5R,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-3,5-dihydroxy-6-(hydroxymethyl)dihydro-2H-pyran-4(3H)-one (5) Compound **19** (14 mg, 0.034 mmol) was dissolved in acetonitrile/water (10/1, 2.0 mL). Then **catalyst A (B,** or **C)** (2.0 mg, ~5 mol%) was added, and the mixture was stirred at room temperature under O_2 atmosphere for 19 h. LC-MS showed the reaction to be completed. After evaporation solvents, the residue was pre-TLC

(MeOH/DCM = 1:10) to produce compound **5** as a white solid (7 mg, 50%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 1H), 7.27 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.48 (d, *J* = 1.6, 9.6 Hz, 1H), 4.27 (dd, *J* = 1.6, 9.6 Hz, 1H), 4.18 (d, *J* = 9.6 Hz, 1H), 4.11-4.02 (m, 3H), 4.00 (q, *J* = 6.8 Hz, 2H), 3.90 (dd, *J* = 4.4, 12.4 Hz, 1H), 3.52-3.48 (m, 1H), 1.40 (t, *J* = 6.8 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 207.56, 157.47, 139.35, 136.28, 134.75, 131.05, 129.90, 129.80, 126.06, 114.55, 84.16, 83.03, 72.71, 63.46, 62.37, 38.39, 14.90; LC-MS (ESI) : 424.39 $[M+NH_4]^+$.

[0171] Example of 3-oxo glucopyranoside (compound 5) synthesis route 2



[0172]

[0173] Step 1: (2R,3S,4S,5R,6S)-2-(((tert-Butyldimethylsilyl)oxy)methyl)-6-(4-methoxyphenoxy)tetrahydro-2H-pyran-3,4,5-triol (5a) To a solution of compound **19b** (3.74 g, 13.1 mmol), imidazole (1.96 g, 28.8 mmol) in DMF (30 mL) was added a solution of TBSCl (2.37 g, 15.7 mmol) in DMF (5 mL) dropwise at 0 °C under a nitrogen atmosphere. After stirring at room temperature for 12 hrs, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (2×30 mL). The organic layer was evaporated and the crude product was purified by column chromatography (200~300 mesh silica gel, eluted with EtOAc/PE = 1:1) to afford compound **5a** as a white solid (3.85 g, 74%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.98 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.30 (d, *J* = 5.2 Hz, 1H), 5.11 (d, *J* = 4.8 Hz, 1H), 5.06 (d, *J* = 5.2 Hz, 1H), 4.68 (d, *J* = 7.6 Hz, 1H), 3.88 (d, *J* = 10.8 Hz, 1H), 3.69 (s, 3H), 3.65-3.58

(m, 1H), 3.34-3.28 (m, 1H), 3.25-3.16 (m, 2H), 3.11-3.07 (m, 1H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); LC-MS (ESI): 418.23 $[M+NH_4]^+$.

[0174] Step 2: tert-Butyldimethyl(((2R,3R,4S,5R,6S)-3,4,5-tris(benzyloxy)-6-(4-methoxyphenoxy)tetrahydro-2H-pyran-2-yl)methoxy)silane (5b) To a solution of compound **5a** (4.4 g, 11 mmol) in DMF (40 mL) was added NaH (60%, 1.76 g, 44 mmol) at 0 °C portionwise. The mixture was stirred at room temperature for 1 hour. BnBr (5.19 mL,44 mmol) was added dropwise and the reaction was stirred at room temperature overnight. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc (3×30 mL). The organic layer was evaporated and the crude product was purified by column chromatography (200~300 mesh silica gel, eluted with EtOAc/PE = 1:5) to afford compound **5b** as a white solid (6.37 g, 86%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 15 H), 7.03 (d, *J* = 9.2 Hz, 2H), 6.80 (d, *J* = 9.2 Hz, 2H), 5.05 (d, *J* = 10.8 Hz, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.88-4.80 (m, 4H), 4.68 (d, *J* = 10.8 Hz, 1H), 3.87-3.85 (m, 1H), 3.77 (s, 3H), 3.71-3.68 (m, 2H), 3.66-3.61 (m, 2H), 3.40-3.68 (m, 1H), 0.89 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H) ; LC-MS (ESI): 688.33 $[M+NH_4]^+$.

[0175] Step 3: (2R,3R,4S,5R,6R)-3,4,5-tris(Benzyloxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-2-ol (5c) To a cooled solution of compound **5b** (5.95 g, 8.88 mmol) in acetonitrile (60 mL), a solution of CAN (14.6 g, 26.6 mmol) in H_2O (15 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 4 hrs and then partitioned between DCM (100 mL) and H_2O (30 mL). The aqueous layer was extracted with DCM (500 mL). The combined organic extracts were washed with $NaHCO_3$ saturated aqueous solution (15 mL), brine (15 mL), dried (Na_2SO_4), and concentrated to produce a residue, which was purified by column chromatography (200~300 mesh silica gel, eluted with EtOAc/PE = 1:3-1:1) to give compound **5c** as a yellow solid (mixture of α and β epimers, 2.01 g, 50%); LC-MS (ESI): 468.21 $[M+NH_4]^+$.

[0176] Step 4: (2R,3R,4S,5R,6R)-3,4,5-tris(Benzyloxy)-6-((tert-butyldimethylsilyloxy)methyl)tetrahydro-2H-pyran-2-ol (5d) To a solution of compound **5c** (1.858 g, 4.13 mmol), imidazole (618 mg, 9.08 mmol) in DMF (30 mL) was added a solution of TBSCl (746 mg, 4.95 mmol) in DMF (5 mL) dropwise at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 12 hrs. Then poured into water (100 mL) and extracted with EtOAc (2×20 mL). The organic layer was evaporated and the crude product was purified by column chromatography (200~300 mesh silica gel, eluted with EtOAc/PE = 1:3) to afford compound **5d** as a yellow solid (mixture of α and β epimers, 1.65 g, 71%); LC-MS (ESI): 582.42 $[M+NH_4]^+$.

[0177] Step 5: (3R,4S,5R,6R)-3,4,5-tris(Benzyloxy)-6-((tert-butyldimethylsilyloxy)methyl)tetrahydro-2H-pyran-2-one (5e) Oxalic chloride (0.27 mL, 3.19 mmol) in anhydrous DCM (5 mL) was added to a solution of DMSO (0.46 mL, 6.39 mmol) in anhydrous DCM (10 mL) at -65 °C under nitrogen atmosphere. After stirring for 30 min at that temperature, a solution of compound **5d** (1.5 g, 2.66 mmol) in anhydrous DCM (15 mL) was added at -65 °C. The reaction mixture was then stirred at -65 °C for 1 h, TEA (1.48 mL, 10.64 mmol) was added dropwise at that temperature. After stirring for 30 min, the mixture was then warmed to -10 °C and quenched with H_2O (15 mL) and extracted with DCM (3×10 mL). The organic extracts were dried over $MgSO_4$, and concentrated to produce a residue, which was purified by chromatography (200~300 mesh silica gel, eluted with EtOAc/PE =1:5) to produce compound **5e** as a colorless oil (1.178 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 15 H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.76 (d, *J* = 10.2 Hz, 2H), 4.66 (d, *J* = 10.2 Hz, 1H), 4.64 (d, *J* = 10.2 Hz, 2H), 4.30-4.26 (m, 1H), 4.07-4.05 (m, 1H), 3.95 (t, *J* = 7.6 Hz, 1H), 3.90 (t, *J*= 7.6 Hz, 1H), 3.86 (dd, *J*= 2.0, 11.6 Hz, 1H), 3.79-3.75 (dd, *J*= 2.0, 11.6 Hz, 1H), 0.85 (s, 9H), 0.03 (s, 6H); LC-MS (ESI): 580.34 $[M+NH_4]^+$.

[0178] Step 6: (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-(((tert-butyldimethylsilyl)oxy)methyl)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran-2-ol (5f) To a solution of 4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (619 mg, 1.91 mmol) in anhydrous PhMe / THF (2:1, 12 mL) was added n-BuLi (2.4M in hexane, 0.8 mL, 1.91 mmol) dropwised at -78 °C under nitrogen. The mixture was stirred at -78 °C for 1 h. A mixture of compound **5e** (978 mg, 1.74 mmol) in anhydrous PhMe / THF (2:1, 12 mL) was added dropwise and stirred -78 °C for another 1 h. Then the mixture was increased from -78 °C to -25 °C , and to the mixture was dropwisely added saturated NH_4Cl solution (20mL) and extracted with DCM (3×15 mL). The organic extracts were dried over $MgSO_4$, and concentrated to produce a residue, which was purified by chromatography (200~300 mesh silica gel, eluted with EtOAc/PE =1:3-1:1) to give compound **5f** as a pale oil (mainly β-epimer, 760 mg, 54%); LC-MS (ESI): 826.34 $[M+NH_4]^+$.

[0179] Step 7: tert-Butyldimethyl(((2R,3R,4R,5S,6S)-3,4,5-tris(benzyloxy)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran-2-yl)methoxy)silane (5g) To a solution of compound **5f** (760 mg, 0.94 mmol) in anhydrous DCM (15 mL) was added Et_3SiH (0.3 mL, 1.88 mmol) and $BF_3{\cdot}Et_2O$ (0.14 mL, 1.13 mmol) dropwise at -20 °C under N_2 atmosphere. The reaction mixture was allowed to stir at -20 °C for 3 hrs. Saturated $NaHCO_3$ aqueous solution (15 mL) was added to the reaction mixture and the organic layer was separated from the aqueous layer. The aqueous layer was extracted with DCM (3×10 mL). The combined organic extracts

were dried over $MgSO_4$, and concentrated to produce a residue, which was purified by chromatography (200~300 mesh silica gel, eluted with PE/EtOAc = 2:1) to produce compound **5g** as a white solid (460 mg, 62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 11H), 7.24-7.19 (m, 5 H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.90-6.87 (m, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 4.88 (d, *J* = 10.4 Hz, 1H), 4.89 (s, 2H), 4.76 (d, *J* = 10.8 Hz, 1H), 4.40 (d, *J* = 10.8 Hz, 1H), 4.14 (d, *J* = 10.4 Hz, 1H), 4.06-4.02 (m, 1H), 3.99-3.91 (m, 4H), 3.88-3.84 (m, 1H), 3.84-3.79 (m, 2H), 3.78-3.73 (m, 1H), 3.39-3.35 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); LC-MS (ESI): 810.32 $[M+NH_4]^+$.

[0180] Step 8: (2R,3S,4R,5R,6S)-2-((tert-butyldimethylsilyloxy)methyl)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)tetrahydro-2H-pyran-3,4,5-triol (5h)

[0181] To a solution of compound **5g** (460 mg, 0.58 mmol), 1,2-dichlorobenzene (426 mg, 2.9 mmol) in EtOAc (12 mL) was added Pd/C (10 wt%; 50 mg) and the mixture was stirred at room temperature for 4 hrs under H_2 balloon. The reaction mixture was filtered through celite and the filtrate was concentrated to give a residue, which was purified by chromatography (200~300 mesh silica gel, eluted with MeOH/DCM =1:30-1:15) to produce compound **5h** as a white solid (236 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.8 Hz, 1H), 7.18-7.16 (m, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 4.04-3.95 (m, 5H), 3.80-3.65 (m, 4H), 3.48-3.42 (m, 5H), 1.39 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.08(s, 3H), 0.06 (s, 3H); LC-MS (ESI): 540.46 $[M+NH_4]^+$.

[0182] Step 9: (2S,3S,5R,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-3,5-dihydroxy-6-(hydroxymethyl)dihydro-2H-pyran-4(3H)-one (5) Compound **5h** (186 mg, 0.356 mmol) was dissolved in acetonitrile/water (12 mL,10:1). Then **catalyst A (B,** or **C)** (19 mg, 5 mol%) was added, and the mixture was stirred at room temperature for 2 days. LC-MS showed the reaction to be completed. After evaporation solvents, the residue was purified by chromatography (200~300 mesh silica gel, eluted with MeOH/DCM =1:10) to produce compound **5** as a white solid (70 mg, 49%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 1H), 7.27 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.48 (d, *J* = 1.6, 9.6 Hz, 1H), 4.27 (dd, *J* = 1.6, 9.6 Hz, 1H), 4.18 (d, *J* = 9.6 Hz, 1H), 4.11-4.02 (m, 3H), 4.00 (q, *J* = 6.8 Hz, 2H), 3.90 (dd, *J* = 4.4, 12.4 Hz, 1H), 3.52-3.48 (m, 1H), 1.40 (t, *J* = 6.8 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 207.56, 157.47, 139.35, 136.28, 134.75, 131.05, 129.90, 129.80, 126.06, 114.55, 84.16, 83.03, 72.71, 63.46, 62.37, 38.39, 14.90; LC-MS (ESI) : 424.39 $[M+NH_4]^+$.

[0183]

[0184] Part II : *In-Vitro* Assay

[0185] Chinese Hamster Ovary (CHO) Cells expressing hSGLT1, hSGLT2 were maintained in Ham's F-12 Nutrient Mixture supplemented with 500 μg/ml hygromycin and 10% FBS using standard cell culture techniques. The cells were plated in tissue culture treated 96-well Isoplate and cultured for 24 hours at 37℃. Then the cells were washed three times with assay buffer KRH-Na^+ (120 mM NaCl, 4.7 mM KCl, 1.2 mM $MgCl_2$, 2.2 mM $CaCl_2$, 10 mM HEPES, PH 7.4 with 1 mM Tris) or KRH-NMG (120 mM NMG, 4.7 mM KCl, 1.2 mM $MgCl_2$, 2.2 mM $CaCl_2$, 10 mM HEPES, PH 7.4 with 1 mM Tris). The sodium-dependent glucose transport assay was initiated by adding 10uCi/ml [^{14}C]-AMG in KRH-Na^+ buffer or KRH-NMG buffer and inhibitors or DMSO vehicle. The assay plates were incubated for 1 h at 37°C. [14C]-AMG-uptake was stopped by adding 100 μL of ice-cold stop buffer (KRH-Na^+ buffer plus 0.5 mM phlorizin). The cells were washed five times with stop buffer and then lysed with 20ul/well ice-cold buffer (100mM NaOH). 80 μl/well Microscint 40 was added and the microtiter plate was counted in a MicroBeta Trilux (PerkinElmer). Dapagliflozin was evaluated in parallel in every assay. A dose-response curve was fitted to an empirical four-parameter model using XL Fit (IDBS, Guilford, U.K.) to determine the inhibitor concentration at half-maximal response (IC_{50}).

[0186] Table 1

Test Compound	hSGLT2 (IC_{50})	hSGLT1 (IC_{50})
1	1-1000 nM	N
2	1-1000 nM	N
3	1-1000 nM	N
4	1-100 nM	>1 μM
5	1-100 nM	>1 μM
6	1-1000 nM	> 5 uM
7	1-100 nM	>1 μM
8	1-1000 nM	> 5 uM
9	1-100 nM	>1 μM
10	1-100 nM	0-1 μM
11	1-100 nM	0-1 μM
12	1-1000 nM	N
13	1-100 nM	>1 μM
14	1-1000 nM	N
15	1-100 nM	N
16	1-100 nM	>1 μM

18	1-1000 nM	N
20	1-100 nM	0-1 μM
21	1-100 nM	>1 μM
22	1-100 nM	>1 μM
23	1-100 nM	>1 μM

[0187] [N] Not detected.

[0188] ***In Vivo* Assay**

[0189] Examples **5**, **13** and **16** were tested in normal rats to assess the control of blood glucose increase in Glucose Tolerance test (OGTT) and/or inhibition of glucose re-absorption via urinary glucose excretion. For the OGTT assay, male Sprague-Dawley rats (~ 250 g) were fasted overnight but had access to water ad libitum. Rats (n = 3 /group) received vehicle or compound by oral gavage. Dosing solutions were 0.2 mg/ml, 0.6 mg/ml, 2 mg/ml and 6 mg/ml for the 1 mg/kg, 3 mg/kg, 10 mg/kg and 30 mg/kg doses respectively. Dosing volumes was 5 ml/kg of body weight of all doses. One group received vehicle, three groups received 3 mg/kg, 10 mg/kg or 30 mg/kg dose of Example **5**, three groups received 3 mg/kg, 10 mg/kg or 30 mg/kg dose of Example **13**, and others received 1 mg/kg, 3 mg/kg or 10 mg/kg dose of Example **16**. The vehicle was 5% 1-methyl-2-pyrrolidinone, 20% polyethylene glycol, and 20 mmol/L sodium diphosphate. One hour after oral administration of compound or vehicle, rats were dosed orally with 40% aqueous glucose solution (2 g/kg). Blood glucose concentration was measured before compound dosing, before the glucose challenge, 15 min, 30 min, 60 min and 120 min post-glucose challenge. Blood glucose was measured using a glucometer (One touch, LifeScan Inc.). The total AUC of blood glucose was calculated to assess the glucose control efficacy of compounds and the results are shown in Table **2**. For the assessment of inhibition of glucose reabsorption via urinary glucose excretion, Male Sprague Dawley rats (~300 g) were singly housed in metabolic cages for urine collection. Compounds (Example **5**) and glucose were dosed as the same as described above. And urine was collected from 0 to 6-h and 6 to 24-h post-glucose challenge. Urine glucose concentration was determined using the Glucose (GO) Assay Kit (Sigma GAGO-20) by measuring absorbance at 540 nm using the plate reader Enspire (PerkinElmer, Inc.). The urine volume was recorded and normalized to body weight using the formula below:

[0190] Normalized urine volume = Urine volume (ml) × 200/rat body weight (g). The total amount of urinary glucose excretion (UGE) was calculated as the product of urine glucose concentration and urine volume using the formula below:

[0191] UGE (mg)/200 g body weight = urinary glucose concentration (mg/dl) × urine volume (dl) × 200/rat body weight (g). Amounts of UGE were obtained from rats for Example **5** by the method described above and are shown in Table **3**.

[0192] Table 2

Compound	Dose (mg/kg)	Mean AUC (-60min~120min) of Blood glucose (mg/dl*min) ± SEM (n=3)
Vehicle	0	21398 ± 2174
Example **5**	3	16281 ± 1419
Example **5**	10	12204 ± 1907
Example **5**	30	9630 ± 984
Example **13**	3	20700 ± 307
Example **13**	10	18770 ± 249
Example **13**	30	17761 ± 1389
Example **16**	1	20102 ± 910
Example **16**	3	18574 ± 838
Example **16**	10	15012 ± 1500
Example **20**	3	13721 ± 1358
Example **20**	10	11055 ± 1056
Example **21**	3	15654 ± 2497
Example **21**	10	14189± 2585
Example **22**	3	16359± 1556
Example **22**	10	10432± 885
Example **23**	3	16583± 2008
Example **23**	10	12759± 706
Canagliflozin, **25**	10	16843± 1211

[0193] Table 3

Compound	Dose (mg/kg)	Assay period	Mean UGE (mg/200g of body weight) ± SEM (n=3)	Mean Urine volume (ml/200g of body weight) ± SEM (n=3)
Vehicle	0	0 – 6 hr	0	0.52 ± 0.76

Example **5**	10	0 – 6 hr	254.4 ± 68.3	3.18 ± 1.20
Vehicle	0	0 – 24 hr	0	3.78 ± 4.08
Example **5**	10	0 – 24 hr	430.9 ± 56.2	10.13 ± 5.32

[0194] Examples **5** and **16** were tested in ZDF rat to assess the control of blood glucose increase in diabetic animals and/or inhibition of glucose re-absorption via UGE. For the acute diabetic rat studies, the ZDF rats were weighed, bled via the tail tip in the fed state, and randomized into four groups (~ 400 g, n = 4 per group). Rats were dosed with vehicle or drug (5ml/kg; 1 mg/kg, 3 mg/kg or 10 mg/kg Example **5**) and placed into metabolism cages. Blood glucose was measured immediately before dosing and at 2, 4, 6, and 24-h post-dose, and the results are shown in Figure **1**. Urine collections were obtained at 6-h and 24-h post-dose. The animals were allowed to re-feed after the 6-h time point. Urine glucose and urine volume data were normalized per 400 g body weight using the formula similar as described above for SD rat studies, and the results are shown in Figure **2**. For the chronic diabetic rat studies, ZDF rats were randomized into several groups (n = 3 per group) and dosed orally with vehicle or drug (5ml/kg; 1 mg/kg or 10 mg/kg Example **5** or **16**) once daily for 7 days. Ad-lib fed blood glucose was measured at the beginning and the end of the experiments, and the results are shown in Table **4**.

[0195] Table 4

Compound	**Dose (mg/kg)**	**Blood glucose (mg/dl) _ Ad-lib feeding**	
		Day 1	**Day 7**
Vehicle-**1**	0	461.1 ± 39.9	448.8 ± 94.6
Example **5**	1	440.3 ± 38.8	390.6 ± 84.0
Example **5**	10	459.5 ± 22.2	317.3 ± 21.0
Vehicle-**2**	0	426.9 ± 3.6	443.1 ± 12.2
Example **16**	1	437.1 ± 15.2	396.6 ± 57.8
Example **16**	10	404.1 ± 28.3	281.4 ± 67.0

[0196] Part III

[0197] 1) **Human Liver Microsome, Rat Liver Microsome and Mouse Liver Microsome Stability**

[0198] Table 5

Cmpd	**HLM**		**RLM**		**MLM**	
	$T_{1/2}$ (min)	**CLint** (uL/min/mg protein)	**$T_{1/2}$** (min)	**CLint** (uL/min/mg protein)	**$T_{1/2}$** (min)	**CLint** (uL/min/mg protein)
1	187	3.70	97.6	7.10	48.1	14.4

2	114	6.10	71.5	9.70	97.6	7.10
5	462.1	1.5	87.7	7.9	45.6	15.2
6	83.5	8.30	59.2	11.7	178	3.90
7	111.8	6.2	79.7	8.7	25.9	26.8
8	105.0	6.6	61.9	11.2	30.4	22.8
9	0.753	921	16.3	42.6	1.50	463
10	99.0	7.00	88.9	7.80	61.3	11.3
11	105	6.60	79.7	8.70	51.3	13.5
13	158	4.40	107	6.50	40.3	17.2
16	108	6.40	73.0	9.50	20.1	34.5
18	1155	0.600	88.9	7.80	117	5.90
20	248	2.80	147	4.70	32.1	21.6
22	385	1.80	578	1.20	277	2.50
23	91.2	7.60	267	2.60	131	5.30

[0199] Note: Incubation Protein Conc = 1mg/mL, Incubation Test Compound Conc. = 1 μM, Incubation Time = 60 min

[0200] 2) **Cytochrome P*450 enzyme* inhibition**

[0201] **Table 6**

CYP	**1A2**	**2D6**	**3A4**	**2C9**	**2C19**
Substrate	Phenacetin (10 μM)	Dextromethorphan (5 μM)	Midazolam (1 μM)	Diclofenac (10 μM)	Omeprazole (0.5 μM)
Inhibitor	Naphthoflavone	Quinidine	Ketoconazole	Sulfaphenazole	Tranylcypromine
Cmpds	IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)
Control	0.014	0.0336	0.0479	0.815	3.19
5	> 10	> 10	> 10	> 10	> 10
6	> 10	> 10	> 10	> 10	> 10
7	> 10	> 10	> 10	> 10	> 10
9	>10	>10	>10	>10	>10
10	>10	>10	>10	>10	>10
11	>10	>10	>10	>10	>10
13	>10	>10	>10	>10	>10
16	>10	>10	>10	>10	>10
18	>10	>10	>10	>10	>10

20	>10	>10	>10	>10	>10
21	>10	>10	>10	>10	>10
22	>10	>10	>10	>10	>10
23	>10	>10	>10	>10	>10

[0202] Note: Incubation Human Liver Microsome Conc = 0.2 mg/mL, Incubation Time = 20 min

[0203] 3) **Plasma Protein Binding Result**

[0204] **Table 7**

	Compounds ID	**Rat PPB %**	**Rat plasma Stability@6 hr (%)**
Control	Phenacetin	53.1	96.7
	Quinidine	72.7	99.8
	Warfarin	99.4	100
Compounds	**24**_3 μM	97.2	72.9
	24_10 μM	96.7	102
	5_3 μM	98.2	29.9
	5_10 μM	97.6	36.1
	7_3 μM	97.2	~ 50
	7_10 μM	97.8	
	25_3 μM	99.2	101
	25_10 μM	99.2	100
	10_3 μM	99.9	65.3
	10_10 μM	99.7	73.0
	11_ 3μM	100	15.2
	11_10 μM	100	29.3
	26_3 μM	96.8	123
	26_10 μM	96.8	110
	13_3 μM	98.1	29.9
	13_10 μM	97.8	46.9
	27_3 μM	92.3	103
	27_10 μM	91.9	105
	18_3 μM	93.5	14.6
	18_10 μM	93.0	21.0

	20_5 μM	94.4	39.9
	20_10 μM	93.7	44.9
	22_1 μM	85.8	78.7
	22_5 μM	86.7	76.9
	22_10 μM	85.9	76.1

[0205] [N] Not detected. Note : Incubation Test Compound Conc = 1 μM or 3 μM or 10 μM, Incubation Time 6 hr.

[0206] **4) <u>Pharmacokinetics Testing in Rats</u>**

[0207] Examples **5**, **7**, **10**, **13**, **16**, **18** was tested in rats to assess pharmacokinetic parameters including maximum concentration (C_{max}), area under the plasma concentration time curve (AUC), clearance (CL), steady state volume of distribution (V_{ss}), half life ($t_{1/2}$), and bioavailability (F). Male Sprague-Dawley rats (~250 g) were used. Rats received the compound by intravenous (IV) or oral gavage (PO) administration and the doses tested including vehicle to formulate dosing solutions are listed in Table **8**.

[0208] Following IV or PO administration, 0.2 ml blood was sampled through eye puncture at various timepoints (Table **8**). Fifty microl aliquots of plasma samples and standards were subjected to protein precipitation with acetonitrile containing an internal standard. Samples were vortexed and centrifuged to obtain supernatant which was analyzed by LC-MS/MS. Analyst (Version 2.6.0) was used to measure peak areas and peak area ratios of analytes to internal standard were calculated. LC-MS/MS conditions are as follows: Mass Spectrometer + Source Type was Thermo TSQ Quantum Discovery Max; HPLC was Finnigan surveyor MS pump; Autosamples was Finnigan surveyor Autosamples; Injection volume was 10.0 microl; A gradient was used with mobile phase A: 5mM ammonium acetate in water; B: Acetonitrile; Flow rate 0.300 ml per minute (Column 3.0 x 30 mm 2.6 micro Kinetex C18 column (phenomenex). Detection mode was negative.

[0209] A calibration curve was constructed from the peak area ratios of standards to the internal standard by applying a weighted linear (1/x2) regression. The dynamic range of the standard curve was 20.00 ng/ml to 5000 ng/ml.

[0210] Phamacokinetic parameters were determined from individual animal data using non-compartmental analysis in phoenix 64 (winNonlin 6.3). Concentrations below the limit of quantification (BLOQ) were recorded as 0 ng/ml for use in calculations.

[0211] The following calculations were used:

[0212] AUC_{last} = Determined using the linear trapezoidal method

[0213] AUC_{inf} = AUC_{last} plus extrapolated area determined by dividing plasma concentration at last time by the slope of the terminal log-linear phase

[0214] CL = Dose/AUC_{inf}

[0215] V_{ss} = CL x MRT

[0216] C_{max} = Recorded directly from plasma concentration time curve

[0217] T_{max} = Recorded directly from plasma concentration time curve

[0218] $t_{1/2}$ = ln (0.5) /slope of the terminal log-linear phase

[0219] F% = AUC_{inf} PO per dose / AUC_{inf} IV per dose

[0220] $C_{(0)}$ = Extrapolated by linear regression from the apparent distribution phase following IV administration

[0221] MRT = AUMC (AUC_{inf})/ AUC_{inf}

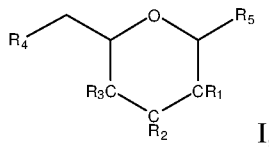
[0222] **Table 8**

Example	Dose (mg/kg)	Route /n	Formulation (v/v/v)	Time Points (h)	Cmax (ng/mL)	AUC_{inf} (hr*ng/mL)	CL (mL/min/kg)	Vss (L/kg)	$T_{1/2}$ (h)	F (%)
5	1.30	iv/ (n=3)	DMSO/ 40%SBEC/ 0.9%NaCl (5/25/70)	1,2,4,8	-	3533	6.13	0.870	1.70	-
	7.55	po/ (n=3)	NMP/ PEG400/ 26.6mM SPP (5/20/75)	2,4,8,24	2442	14232	-	-	2.79	69.4
	3.25	po/ (n=3)	0.2% CMC + 0.2% TW80	2,4,8	1051	5739	-	-	2.43	65.0
7	1.70	iv/ (n=3)	DMSO/ PEG400/ 40%SBECD/ 0.9%NaCl (5/10/45/40)	0.083,0.25, 0.5, 1, 2, 4	-	1583	18	1.34	0.898	-
	11.69	po/ (n=3)	0.5% MC	2,4,8	350.8	2172	-	-	3.75	20
10	2.00	iv/ (n=3)	DMSO/ Cremophor/ 0.9%NaCl (5/5/90)	2,4,8	-	2898	11.50	2.313	2.45	-
	5.00	po/ (n=3)	NMP/ PEG400/ 26.6mM SPP (5/20/75)	2,4,8	458	3095	-	-	3.06	39
13	1.40	iv/ (n=3)	DMSO/ 40%SBECD/ 0.9%NaCl (5/25/70)	2,4,8	-	1958	11.92	3.121	3.23	-
	4.65	po/ (n=3)	NMP/ PEG400/ 26.6mM SPP (5/20/75)	2,4,8	635	4110	-	-	3.52	59

16	2.00	iv/ (n=3)	DMSO/ 40%SBECD/ 0.9%NaCl (5/25/70)	0.25,0.5, 1,2,4	-	2026	16.45	1.145	0.93	-
	5.00	iv/ (n=3)	DMSO/ 40%SBECD/ 0.9%NaCl (5/25/70)	2,4,8	-	5968	14	1.18	1.25	-
	10.00	po/ (n=3)	NMP/ PEG400/ 26.6mM SPP (5/20/75)	4,8,24	590	6226	-	-	6.06	52
18	2.00	iv/ (n=3)	DMSO/ 40%SBECD/ 0.9%NaCl (5/25/70)	0.5,1,2,4,8	-	1837	18.14	1.344	1.01	-
	10.00	po/ (n=3)	NMP/ PEG400/ 26.6mM SPP (5/20/75)	1,2,4,8,24	733	3851	-	-	3.68	42
20	2.00	iv/ (n=3)	DMSO/ 40%SBECD/ 0.9%NaCl (5/25/70)	0.083,0.25, 0.5, 1, 2, 4		2098	15.89	1.17	1.03	
	10.00	po/ (n=3)	NMP/ PEG400/ 26.6mM SPP (5/20/75)	0.083,0.25, 0.5, 1, 2, 4, 8	2129	9237			2.29	88
22	2.00	iv/ (n=3)	DMSO/ 40%SBECD/ 0.9%NaCl (5/25/70)	0.083,0.25, 0.5, 1, 2, 4, 8		2365	35.24	6.32	3.48	
	10.00	po/ (n=3)	NMP/ PEG400/ 26.6mM SPP (5/20/75)	0.083,0.25, 0.5, 1, 2, 4, 8, 24	2363	8019			5.33	68

CLAIMS:

1. A glucopyranoside compound of formula I:



I,

wherein:

one of R1-R3 is oxo and two of R1-R3 are independently H, F, –OR6, wherein each R6 is independently H, methyl or acetyl (CH_3CO-);

R4 is H, F or OR7, where R7 is H, methyl or acetyl (CH_3CO-);

R5 is aryl or heteroaryl,

or a salt or acetate thereof.

2. The compound of claim 1 wherein:

R2 or R3 is oxo;

R2 is oxo;

two of R1-R3 are independently F or –OR6, wherein each R6 is independently H, methyl or acetyl (CH_3CO-), and R4 is F or OR7, wherein R7 is H, methyl or acetyl (CH_3CO-);

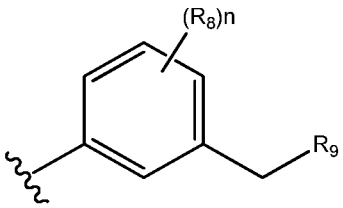
two of R1-R3 are independently –OR6, wherein each R6 is independently H, methyl or acetyl (CH_3CO-), and R4 is OR7, wherein R7 is H, methyl or acetyl (CH_3CO-);

two of R1-R3 are independently –OR6, wherein each R6 is H or acetyl (CH_3CO-), and R4 is OR7, wherein R7 is H or acetyl (CH_3CO-); and/or

two of R1-R3 are independently –OR6, wherein each R6 is H, and R4 is OR7, wherein R7 is H.

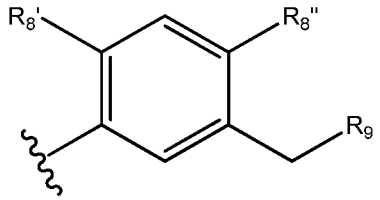
3. The compound of claim 1 wherein R5 is substituted phenyl.

4. The compound of claim 1 wherein R5 is substituted phenyl of formula:



wherein each R8 is a hydrocarbon or heteroatom-containing functional group, R9 is aryl and n is 0, 1, 2, 3 or 4, wherein R8 can also bind C1 of the glucopyranoside ring.

5. The compound of claim 4 wherein R5 is substituted phenyl of formula:



wherein $(R8)_n$ is R8' and R8" and

R8" is H, halide, lower alkyl, lower alkenyl, lower alkynyl or lower alkyloxy, and

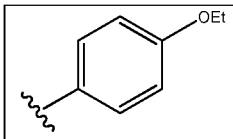
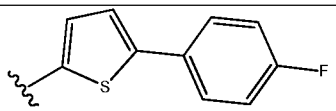
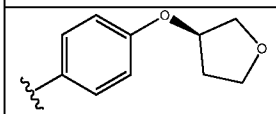
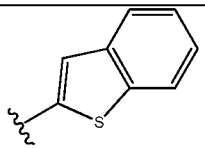
R8' is H, halide, lower alkyl, lower alkenyl, lower alkynyl or lower alkyloxy, wherein the lower alkyloxy also binds C1 of the glucopyranoside ring.

6. The compound of claim 5 wherein R9 is substituted or unsubstituted, homo- or hetero, 5- or 6-membered cyclic or 9 or 10 membered bi-cyclic aryl.

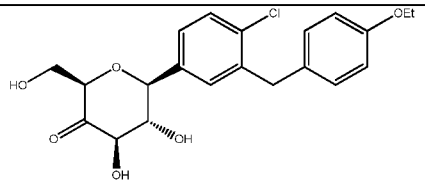
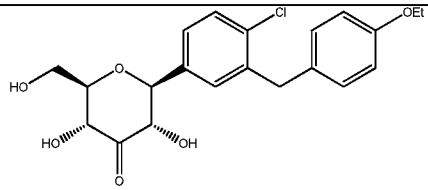
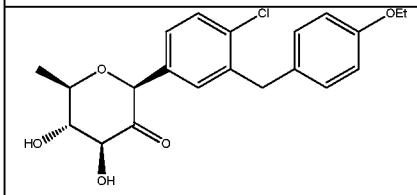
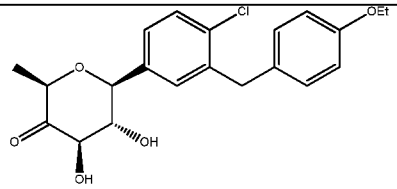
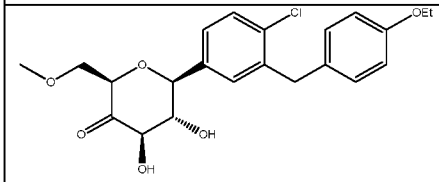
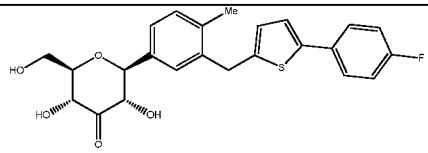
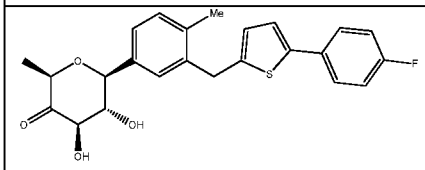
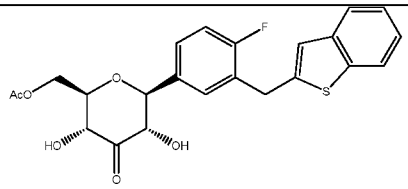
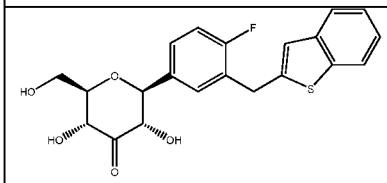
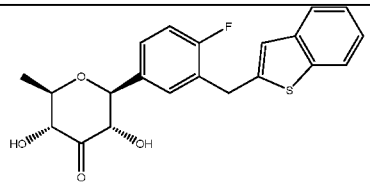
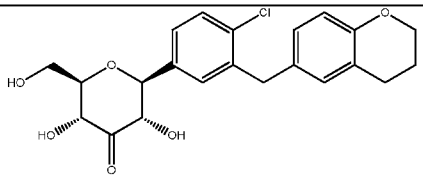
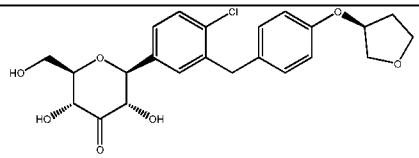
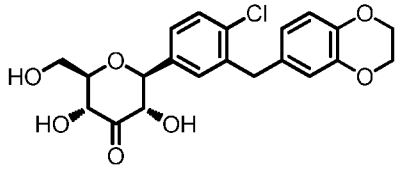
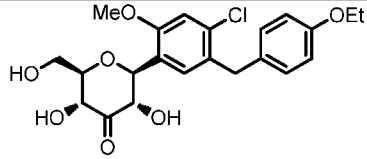
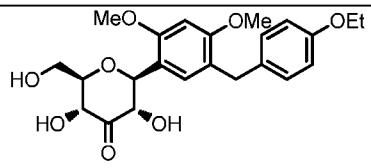
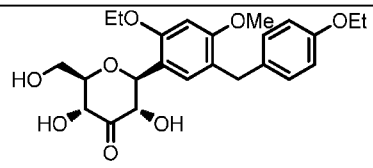
7. The compound of claim 5 wherein R9 is substituted or unsubstituted:

phenyl,	benzopiperidin-6-yl,
pyrrol-2-yl,	3,4-dihydro-2H-benzo[b][1,4]oxazine-7-yl
furan-2-yl,	2,3-dihydrobenzo[b][1,4]dioxin-6-yl,
thiophen-2-yl,	Indolin-5-yl, or 5-indolinyl
chroman-6-yl,	2,3-dihydrobenzofuran-5-yl.

8. The compound of claim 5 wherein R9 is:

 4-ethoxyphenyl;	 4-fluorophenyl thiophen-2-yl;
 tetrahydrofuran-3-yloxy-phenyl; or	 benzo[b]thiophen-2-yl.

9. The compound of claim 1 of formula:

 4;	 5;
 6;	 7;
 8;	 10;
 11;	 12;
 13;	 14;
 16;	 18.
 20;	 21;
	

22;	23.

10. A 2-aryl, 6-methyl-β-dihydro-pyran-one compound, wherein the methyl may be substituted, or salt thereof.

11. The compound of claim 10 that is a 3-oxo-glucopyranoside or 4-oxo-glucopyranoside.

12. The compound of claim 10 wherein the aryl is substituted phenyl.

13. The compound of claim 10 wherein the aryl is 3-(methyl-aryl)5-(lower alkyl) phenyl, wherein the methyl-aryl is methyl-(substituted or unsubstituted, homo- or hetero, 5- or 6-membered cyclic or 9 or 10 membered bi-cyclic aryl).

14. The compound of claim 10 wherein the aryl is 3-(methyl-aryl)5-(lower alkyl) phenyl, wherein the methyl-aryl is methyl-(X), wherein X is:

phenyl,	1,2,3,4-tetrahydroquinolin-6-yl,
pyrrol-2-yl,	3,4-dihydro-2H-benzo[b][1,4]oxazine-6-yl
furan-2-yl,	2,3-dihydrobenzo[b][1,4]dioxide-6-yl,
thiophen-2-yl,	Indolin-5-yl, or
chroman-6-yl,	2,3-dihydrobenzofuran-5-yl.

15. The compound of claim 10 wherein the aryl is:
4-ethoxyphenyl;
4-fluorophenyl thiophen-2-yl;
benzo[b]thiophen-2-yl;
tetrahydrofuran-3-yloxy-phenyl; or
chroman-6-yl-phenyl.

16. An acetate of a compound of any of claims 1-15.

17. A compound of any of the Tables A, B, C or D, or an acetate or salt thereof.

18. The compound of any of claims 1-17 that is a sodium-glucose linked transporter-1 (SGLT2) inhibitor.

19. A pharmaceutical composition comprising a compound of any of claims 1-18 in unit dosage form.

20. A pharmaceutical composition comprising a compound of any of claims 1-18 and a different anti-diabetes drug

21. A method of using a compound of any of claims 1-18 or composition thereof comprising administering it to a person determined to be in need thereof.

22. A method of using a compound of any of claims 1-18 or composition thereof comprising administering it to a person determined to be in need thereof and detecting a resultant therapeutic effect.

23. Use in the manufacture of a medicament a compound of any of claims 1-18.

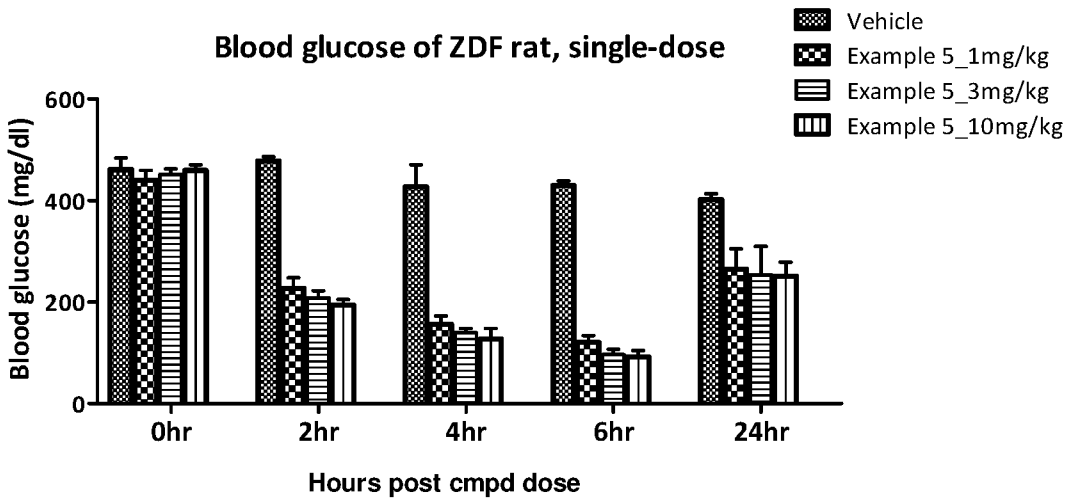

Blood glucose of ZDF rat, single-dose
Vehicle
Example 5_1mg/kg
Example 5_3mg/kg
Example 5_10mg/kg
Blood glucose (mg/dl)
600
400
200
0
0hr
2hr
4hr
6hr
24hr
Hours post cmpd dose

Fig. 1

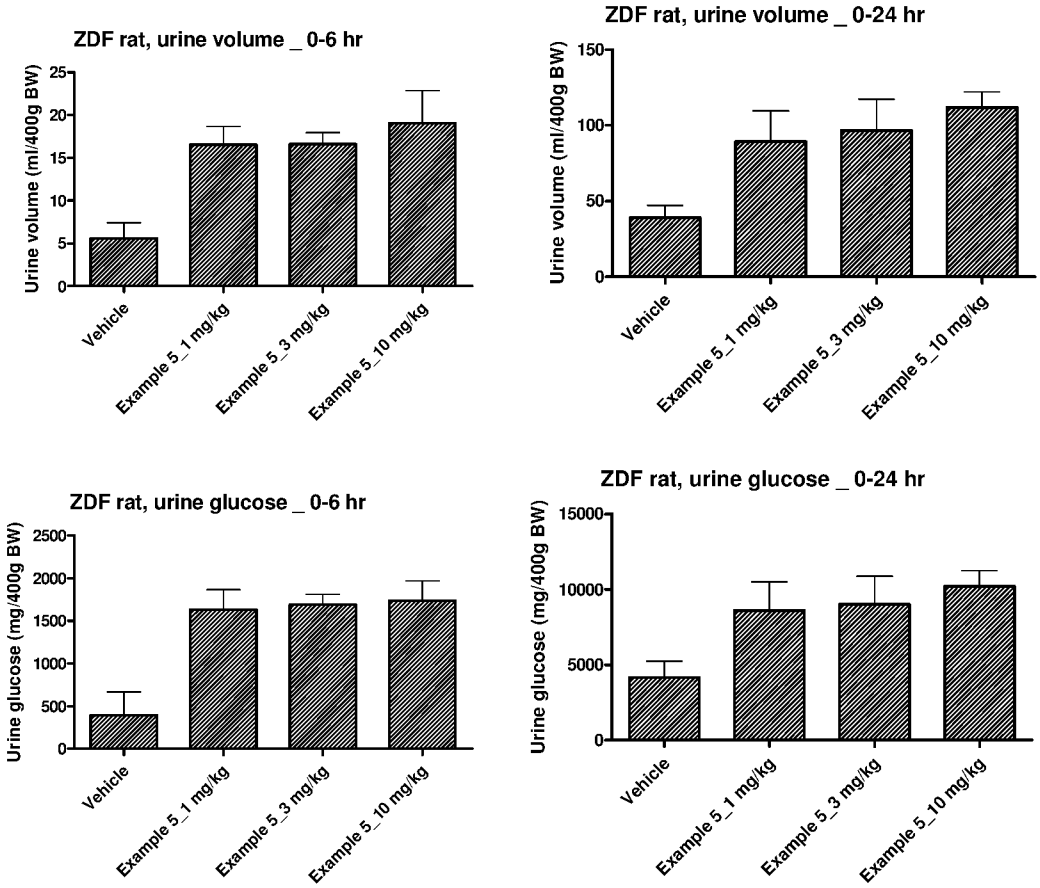

ZDF rat, urine volume _ 0-6 hr
Urine volume (ml/400g BW)
ZDF rat, urine volume _ 0-24 hr
Urine volume (ml/400g BW)
ZDF rat, urine glucose _ 0-6 hr
Urine glucose (mg/400g BW)
ZDF rat, urine glucose _ 0-24 hr
Urine glucose (mg/400g BW)
Vehicle
Example 5_1 mg/kg
Example 5_3 mg/kg
Example 5_10 mg/kg

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/089492

A. CLASSIFICATION OF SUBJECT MATTER

C07D 307/10(2006.01)i; C07D 307/30(2006.01)i; C07H 7/04(2006.01)i; A61K 31/351(2006.01)i; A61P 3/10(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D; C07H; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI,EPODOC,CNKI,CNABS,REGISTRY(STN),CAPLUS(STN);glucopyranos+,glucoside,aryl,aromatic,fluoro+,+diabet?, obesity,SGLT,1376624-31-5,1376624-36-0,1376624-41-7,structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	CN 104761523 A (TIANJIN INSTITUTE OF PHARMACEUTICAL RESEARCH) 08 July 2015 (2015-07-08) description, pages 4-12, examples 1-18	1-23
X	ACS. "1376624-31-5/RN, 1376624-36-0/RN and 1376624-41-7/RN" *STN(REGISTRY)*, 08 June 2012 (2012-06-08), pages 2-3	1-12, 15, 17-18
A	WO 2009/100936 A2 (SANOFI-AVENTIS) 20 August 2009 (2009-08-20) the whole document	1-23
A	WO 2004/080990 A1 (YAMANOUCHI PHARMACEUTICAL CO., LTD) 23 September 2004 (2004-09-23) the whole document	1-23
A	WO 2004/063209 A2 (BRISTOL-MYERS SQUIBB COMPANY) 29 July 2004 (2004-07-29) the whole document	1-23

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2015	**17 December 2015**

Name and mailing address of the ISA/CN	Authorized officer
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China**	**FENG,Qingwei**
Facsimile No. **(86-10)62019451**	Telephone No. **(86-10)61648375**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/089492

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **21-22**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 21-22 are directed to a method of treatment. The search report has been carried out and based on the use of the compound or composition in manufacturing medicaments.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2015/089492

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	104761523	A	08 July 2015	None			
WO	2009/100936	A2	20 August 2009	US	2011059910	A1	10 March 2011
				WO	2009100936	A3	22 October 2009
				EP	2268653	A2	05 January 2011
				CN	101998962	A	30 March 2011
				JP	2011511820	A	14 April 2011
				KR	20100121615	A	18 November 2010
WO	2004/080990	A1	23 September 2004	KR	101001850	B1	17 December 2010
				KR	20080072933	A	07 August 2008
				US	7772407	B2	10 August 2010
				US	2007161787	A1	12 July 2007
				US	7977466	B2	12 July 2011
				JP	4913104	B2	11 April 2012
				CN	1802366	B	22 December 2010
				EP	1980560	B1	25 May 2011
				CN	1802366	A	12 July 2006
				US	2006122126	A1	08 June 2006
				JP	4222450	B2	12 February 2009
				EP	1609785	A1	28 December 2005
				KR	20060002818	A	09 January 2006
				JP	2009046489	A	05 March 2009
				EP	1980560	A3	29 October 2008
				US	2009069252	A1	12 March 2009
				KR	101001848	B1	17 December 2010
				US	7202350	B2	10 April 2007
				EP	1980560	A2	15 October 2008
WO	2004/063209	A2	29 July 2004	US	7375213	B2	20 May 2008
				EP	1581543	A2	05 October 2005
				JP	2006516257	A	29 June 2006
				CN	100391963	C	04 June 2008
				CN	1756759	A	05 April 2006
				CN	101260130	A	10 September 2008
				US	2004138439	A1	15 July 2004
				KR	20050090437	A	13 September 2005
				WO	2004063209	A3	12 May 2005